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Cuijpers, P.

published in

Dialogues in Clinical Neuroscience
2009

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Cuijpers, P. (2009). Prevention: an achievable goal in personalized medicine. *Dialogues in Clinical Neuroscience*, 11(4), 445-454. http://www.dialogues-cns.org/brochures/43/html/43_3.asp

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Dear Colleagues,

In medicine, knowledge of the disease and an understanding of its mechanisms are required; personalized medicine is aimed at determining to what extent the pathology, as well as its treatment, is linked to the individual person.

The symptomatic expression of a disease can differ from one patient to the next; various investigative methods can lead to development of an individual typology, and to identification of particular groups in terms of clinical picture or treatment response.

Certain mechanisms are a function of background factors and environmental influences; it is assumed that these aspects have a determinant influence on the disease, on its course, and possibly on its reaction to various therapeutic approaches.

Finally, the course of the disease in response to treatment can vary from one subject to another (genetic, enzymatic and metabolic aspects, etc).

The tools we have currently available for clinical and biological investigations, and for imaging, allow us to characterize individuals more effectively, and to highlight particular profiles. These specifications are the basis of personalized medicine, which can be applied in specific ways in a number of different fields, whether diagnostic, exploratory, or therapeutic.

In terms of recent developments in modern medicine, it would be a huge task to cover all the fields concerned. In the current issue we have chosen to give examples of possible applications of this approach, without attempting to exhaustively cover all the aspects of this subject.

We would like to warmly thank Prof Barry Lebowitz, who coordinated this issue brilliantly, Dr Rajesh Parikh who assisted him in this, and all the authors of this complex review.

Sincerely yours,

Jean-Paul Macher, MD

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Contributors



Daniel J. Müller, MD

Author affiliations: Pharmacogenetics Research Clinic, Neurogenetics Section, Centre for Addiction and Mental Health, University of Toronto, Canada



Gregory J. Downing, DO, PhD

Author affiliations: Project Director, Personalized Health Care Initiative, Office of the Secretary, Department of Health and Human Services, Washington, DC, USA



Michael Brammer, PhD

Author affiliations: Centre for Neuroimaging Sciences, Institute of Psychiatry, Kings College, London, UK



Jens Benninghoff, MD

Author affiliations: Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany



Anil K. Malhotra, MD

Author affiliations: Center for Translational Psychiatry, Feinstein Institute for Medical Research; Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore – Long Island Jewish Health System, Glen Oaks, NY, USA; Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine, Bronx, NY, USA



Francis E. Lotrich, MD, PhD

Author affiliations: Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, USA



Kathinka Evers, PhD

Author affiliations: Centre for Research Ethics & Bioethics, Uppsala University, Sweden



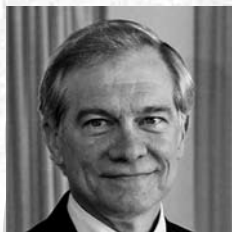
Andrew F. Leuchter, MD

Author affiliations: Laboratory of Brain Behavior, and Pharmacology, and the Depression Research and Clinical Program, Semel Institute for Neuroscience and Human Behavior at UCLA, and the Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California, USA



Pim Cuijpers, PhD

Author affiliations: Department of Clinical Psychology and EMGO Institute, VU University Amsterdam, The Netherlands



Robert E. Drake, PhD

Author affiliations: Dartmouth Psychiatric Research Center, Lebanon, New Hampshire, USA



Nancy F. Stimson, MLS

Author affiliations: Biomedical Library, University of California, San Diego, La Jolla, California, USA

In this issue...

"Every so often, a scientific advance offers new opportunities for making real advances in medical care."¹ The clinical practice of medicine is facing dramatic change and new opportunities. The worldwide investment in biomedical research by governments, foundations, and the private sector, measurable in hundreds of billions of dollars (US), have produced new tools and new approaches that are truly transformational. For disorders of the brain, new tools are yielding new hypotheses to guide treatment discovery and for tailoring treatments to specific patients. This transformation will change the focus of medicine to a more proactive strategy. New structural and functional imaging technologies, in combination with genomic, proteomic, and many other "-omics" methodologies, will create opportunities for selection of "personalized" clinical approaches, rather than the reliance on "one size fits all" treatment strategies. Stem cell approaches have the potential for reversing the neuroanatomic foundation of brain disorders.

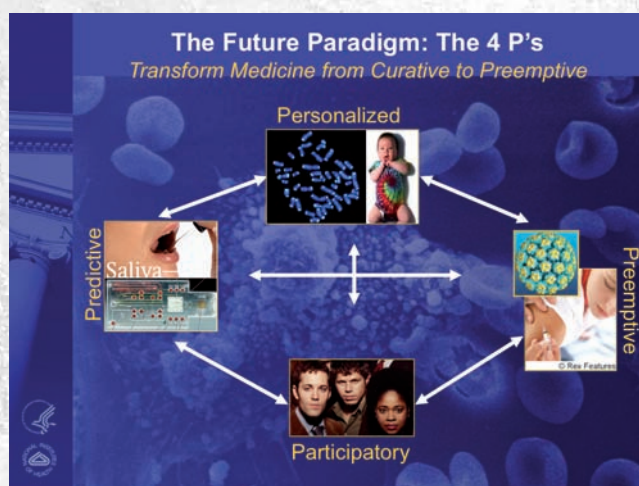


Figure 1, generously provided by the Office of the Director of the US National Institutes of Health (NIH), presents the potential of personalized medicine in what has come to be called the 4P model. In this approach, targets of intervention are broadened beyond treatment response and remission to disease prevention and disruption/reversal of clinical course (*preemption*). The selection of treatments is based upon predictive models and strategies that yield a tailored (*personalized*) approach. The informed and activated patient is a critical part of the transformation of medicine. Thanks to advances in information technology, and to greater acceptance of a "shared decision making"

approach to treatment, medicine is becoming more interactive. The *participatory* aspect of medicine is changing the nature of the doctor-patient relationship.

Personalized medicine is very much a work in progress. We have assembled an outstanding group of international scholars and policy makers to provide a snapshot of this topic. The Editorial Board thanks each of the contributors for their thoughtful papers. The papers as a whole give us much to anticipate as this revolution in medicine unfolds for the benefit of our patients.

The issue begins with an overview of the *State of the art* by Prof Bruce Pollock and colleagues (p 363). The paper contrasts the practice of "average" medicine with a more tailored approach that uses brain imaging, pharmacology, and genetics as markers of treatment response and adverse events. They conclude that no single method is optimal and that multimodal approaches have the greatest potential for moving the field forward.

Interest in the development of personalized medicine is a topic of interest for those at the highest levels of health policy. It is a privilege for *DCNS* to present the first *Special article* we have published. Dr Gregory Downing (p 377), Director of the Personalized Healthcare Initiative of the US Department of Health and Human Services, characterizes personalized medicine as a "disruptive" innovation. He describes the essential role of information technology (health IT) and discusses the substantive thinking on US policy and regulation in personalized medicine (see, for example, ref 2).

Two papers on *Translational research* highlight some of the complex methodological challenges being addressed in the field. Prof Michael Brammer (p 389) illustrates the potential applications of structural and functional magnetic resonance imaging (MRI and fMRI) in personalized medicine and proposes some innovative analytic methods, based on machine learning approaches from the field of artificial intelligence that will facilitate use of these approaches. The paper by Prof Jens Benninghoff (p 397) introduces approaches of stem cell biology and anticipates a future where processes of neurogenesis will become a standard of treatment.

Two papers on *Pharmacological aspects* illustrate the potential of pharmacogenetics. The first, by Profs Todd

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Lencz and Anil Malhotra (p 405), examines the important topic of pharmacogenomic correlates of antipsychotic-induced side effects. They describe the limits of a candidate gene approach and describe new methodological strategies to accelerate developments in the field. The paper by Prof Francis Lotrich (p 417) provides another example of the value of a pharmacogenetic approach in its use in target identification for treatment development. He concludes that identification of modifiable risk factors that is made possible by pharmacogenetics opens the opportunity for preventive intervention.

The prospects of more personalized approaches to medicine are exciting and challenging. At the same time, there are very real possibilities of overpromising (see, for example, ref 3) and misrepresenting the value of these approaches. The **Clinical research** section begins with an article by Prof Kathinka Evers (p 427) that explicates these bioethical concerns. She concludes by alerting us to the possibility of exaggeration of promises and to the need for rigorous cost benefit evaluation of these proposed approaches before adoption (see, for example, ref 4). Moving to clinical or patient-oriented research, Prof Andrew Leuchter and colleagues (p 435) identify a set of clinical and brain function (quantitative electroencephalographic) predictors of treatment response and propose the concept of "response endophenotypes" for this class of predictors. Their approach illustrates many aspects of the possible benefits of tailored approaches to personalized treatment and suggests the possibility of revising the methodology of the randomized clinical trial to establish treatment safety and efficacy. Prof Pim Cuijpers (p 447) proposes a new approach to prevention. A major focus of the paper is innovative use of statistical methods to identify target groups for preventive intervention. He concludes that pre-

vention is currently achievable and that Web-based approaches may make such interventions accessible to broad populations. Prof Robert Drake and colleagues (p 455) summarize their pioneering studies of shared decision making. They make the convincing case for the essential role of shared decision making in the development of personalized mental health care, and identify major barriers that currently inhibit the full implementation of this approach. They identify a number of important research questions that could advance the field and describe the needs for further development from the decision sciences and in the areas of education of clinicians and patients.

Our understanding of personalized medicine and its various component parts is evolving rapidly. Contributions are coming from all over the world and in many different formats. The concluding paper in this issue, a **Brief report** by Nancy Stimson, MLS (p 464), describes the electronic resources that are available and provides guidance on the selection of key words and search strategies. Keeping abreast of this information is a great challenge for the active investigator, teacher, and clinician. She concludes with the recommendation that, when possible, information professionals be involved in the development of efficient search and update strategies.

We are very early in the development of personalized medicine. Already there are a few examples around use of medications.⁵⁻⁸ More will doubtless come. Right now, the use of any of the genomic, imaging, or stem cell approaches discussed in this issue is best seen as exploratory research. We look forward to the time in the not-so-distant future when we will be able to use the technologies of personalized medicine to enhance our research and to optimize our care of patients.

Barry D. Lebowitz, PhD; Rajesh Parikh, MD

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State of the art

The intersection of pharmacology, imaging, and genetics in the development of personalized medicine

Philip Gerretsen, MD, MSW; Daniel J. Müller, MD; Arun Tiwari, PhD; David Mamo, MD, MSc; Bruce G. Pollock, MD, PhD



We currently rely on large randomized controlled trials and meta-analyses to make clinical decisions; this places us at a risk of discarding subgroup or individually specific treatment options owing to their failure to prove efficacious across entire populations. There is a new era emerging in personalized medicine that will focus on individual differences that are not evident phenomenologically. Much research is directed towards identifying genes, endophenotypes, and biomarkers of disease that will facilitate diagnosis and predict treatment outcome. We are at the threshold of being able to predict treatment response, primarily through genetics and neuroimaging. In this review we discuss the most promising markers of treatment response and adverse effects emerging from the areas of pharmacogenetics and neuroimaging in depression and schizophrenia.

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Dialogues Clin Neurosci. 2009;11:363-376.

Keywords: *personalized medicine; pharmacogenetics; neuroimaging; antipsychotic; antidepressant; treatment response; adverse effect; depression; schizophrenia*

Author affiliations: Multimodal Imaging Group, (Philip Gerretsen); Multimodal Imaging Group, Division of Geriatric Psychiatry (David Mamo), Centre for Addiction and Mental Health, University of Toronto, Canada; Pharmacogenetics Research Clinic, Neurogenetics Section (Daniel J. Müller); Neurogenetics Section (Arun Tiwari), Centre for Addiction and Mental Health, University of Toronto, Canada; Division of Geriatric Psychiatry, Centre for Addiction and Mental Health, University of Toronto, Canada (Bruce G. Pollock)

Since the serendipitous discoveries of chlorpromazine and imipramine, the precursors of current antipsychotics and antidepressants, respectively, we have made arguably few strides towards the improvement of clinical outcomes. Our major gains have been in the area of pharmacotherapy acceptance and tolerability. The development of serotonin reuptake inhibitors has dramatically reduced the side effects and lethality in overdose of commonly prescribed antidepressants. Similarly, second-generation antipsychotics have significantly decreased the incidence of extrapyramidal symptoms (EPS), including tardive dyskinesia and parkinsonism, but at the same time have increased the long-term likelihood of mortality and morbidity secondary to adverse metabolic effects.

We remain in an era of uncertainty with regard to the underpinnings of individual variability in order to preemptively differentiate treatment responders from non-responders. Our current evidence-based medicine relies on large randomized control trials and meta-analyses—*average medicine*, which ignores individual differences. This dependence on large group analyses places us at a risk of discarding subgroup-specific treatment options owing to their failure to prove efficacious across entire populations.¹

There is a new era emerging in psychiatry of personalized medicine that will focus on individual differences not evident phenomenologically. Much research is directed towards the identification of genes, endophenotypes, and

Address for correspondence: Bruce G. Pollock, MD, PhD, FRCPC, Vice President, Centre for Addiction and Mental Health Research, Sandra A. Rotman Chair in Neuropsychiatry, Rotman Research Institute, Professor and Head Division of Geriatric Psychiatry, University of Toronto, Faculty of Medicine, 33 Russell Street, Room T-109, Toronto, Ontario, Canada, M5S 2S1 (e-mail: bruce_pollock@camh.net)

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Selected abbreviations and acronyms

5-HT	<i>serotonin</i>
5-HTTLPR	<i>serotonin transporter-linked polymorphic region</i>
ACC	<i>Anterior cingulate cortex</i>
BDNF	<i>brain-derived neurotrophic factor</i>
CYP	<i>cytochrome P450</i>
PM	<i>poor drug metabolizer</i>
UM	<i>ultrarapid drug metabolizer</i>

biomarkers of disease that will facilitate diagnosis and predict treatment outcome. Pharmacogenetic studies that explore the role of an individual's genetic makeup in determining the effectiveness of pharmacotherapy are of increasing interest. The rationale for the hypothesized

role of pharmacogenetics is based on observations made in family and twin studies, where closely related relatives tend to show similar response or side-effect patterns (reviewed in ref 2). All proteins, including those involved in the metabolism and central effects of pharmaceuticals, can differ as a result of naturally occurring variability in the DNA sequence of the associated gene. This has led investigators to study gene variants for their association with antipsychotic drug outcome. Gene variants (ie, alleles or polymorphisms) that code for the enzymes responsible for drug metabolism can affect pharmacokinetics, and therefore the amount of drug available in the body to elicit a response. In addition, gene variants can affect pharmacodynamics, the therapeutic effect of a drug in the target organ (*Figure 1*, "PK and PD"). Representative

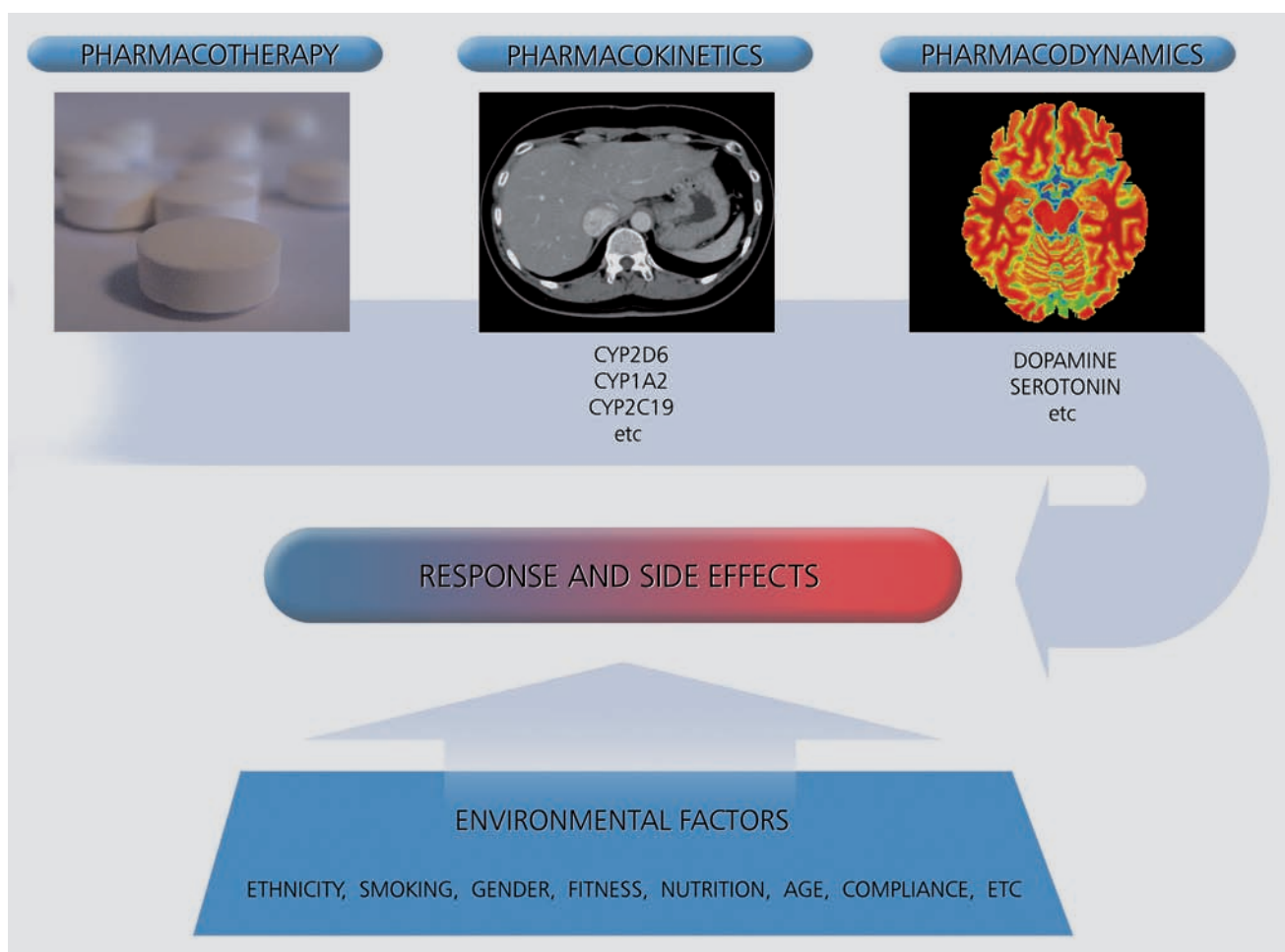


Figure 1. The influence of pharmacokinetic, pharmacodynamic and environmental factors on pharmacotherapy response and side effects (source: www.silvermedia.ca).

examples in breast cancer research include the overexpression of the HER2 gene, a positive predictor of response to the drug trastuzumab (Herceptin), and the predictive value of active cytochrome P450 (CYP) 2D6 alleles in tamoxifen discontinuation.³

In psychiatry, we lack basic laboratory investigations to diagnose mental illness, let alone genetic advances to guide treatment. A primary goal of current research is to characterize the etiologies and biological susceptibilities of heterogeneous, complex conditions, such as depression and psychosis. We are at the threshold of being able to predict treatment response, primarily through genetics and neuroimaging.

Personalized medicine in psychiatry is a broad topic. As such, we will confine our review to the most promising markers of treatment response and adverse effects emerging from the areas of pharmacogenetics and neuroimaging in depression and schizophrenia.

Genetics of antipsychotic drug metabolism, response, and side effects in schizophrenia

Antipsychotic drugs remain the cornerstone of treatment in schizophrenia. However, more than 20% of patients do not initially respond to treatment with drug therapy.⁴ In addition to lack of response, many patients discontinue their medication due to side effects, which can have serious and devastating consequences.⁵

In the following sections we discuss the genetics of antipsychotic drug metabolism, response, and side effects in schizophrenia.

Genetics of antipsychotic drug metabolism

The vast majority of antipsychotic drugs are metabolized by the liver enzymes CYP2D6 and CYP2C19, which play critical roles in determining plasma drug levels. Gene variants that confer altered enzymatic activity influence plasma drug levels, and therefore can predict effective drug doses and potential side effects.

The CYP2D6 gene codes for an enzyme that is responsible for metabolizing the majority of antipsychotic medications.⁶ This enzyme shows genetic variability in activity and is highly polymorphic, with over 70 single nucleotide polymorphisms (SNPs) and copy number variations (CNVs).⁷ These variations can influence antipsychotic drug activity and a patient's ability to metabolize them. Individuals can be classified, based on

their gene polymorphisms, as poor (PM), intermediate (IM), extensive/normal (EM), or ultrarapid drug metabolizers (UM).⁸ The frequency of PMs, IMs, EMs, and UMs varies across ethnicities. For example, Europeans show the highest frequency of CYP2D6 PMs and African-Americans show the highest frequency of CYP2D6 UMs.⁹

In theory, the risk of side effects may be higher in individuals with compromised drug metabolism capabilities because of higher drug plasma levels.¹⁰ Alternatively, drug plasma levels may be lower and medications, as a result, less efficacious in individuals with high enzymatic activity.¹¹ The vast majority of individuals will have no or little impaired enzyme activity (ie, are IM or EM). However, it may be extremely valuable for those individuals who show impaired (PM) or markedly increased activity (UM) to have this information taken into consideration when selecting antipsychotic medication, determining appropriate dosage, or interpreting plasma levels in the context of drug monitoring.

Estimated dose adjustments for antipsychotics have been described based on an individual's metabolizer status.¹² CYP2D6 and CYP2C19 diagnostic testing is FDA approved with the Roche AmpliChip®, but is also available at decreasing costs every year through other companies. Importantly, results from genotyping analyses are only one factor affecting drug plasma levels and should be considered in conjunction with other important criteria, such as comedication, smoking, and diet.⁶

Genetics of antipsychotic treatment response

Another important focus of investigation has been antipsychotic drug response in schizophrenia. The first-generation studies exploring the genetics of antipsychotic treatment outcome were published in the early to mid 1990s. They were performed with small sample sizes and included patients treated mainly with clozapine, but not exclusively. The most interesting findings, albeit mixed, were obtained for the serotonin 2A (5-HT_{2A}) and the dopamine 2 (DRD2) receptor gene polymorphisms.¹³ These results suggested that the effect size of these polymorphisms is low and that other factors, including other genes and gene variants, are likely to be involved.

Second-generation studies have included larger samples, more sophisticated analyses, and multiple polymor-

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phisms, which allow for the investigation of haplotypes and genome-wide associations. These continue to produce promising results for the 5-HT2A and DRD2 gene polymorphisms. A comprehensive analysis which included 12 DRD2 gene polymorphisms in a sample of 232 well-characterized subjects identified protective haplotypes in both Europeans and African-Americans.¹⁴ A review by Arranz et al concluded that the -141C/T polymorphism in the DRD2 gene is of particular significance due to its association with treatment outcome in two independent samples.² A more recent meta-analysis of almost 700 individuals supported the association between the -141C/T polymorphism and antipsychotic drug response.¹⁵ Intriguingly, this polymorphism is located in the promoter region and could have regulatory effects in addition to functional relevance. Although the role of the DRD2 gene in antipsychotic response is not conclusive, these findings are of particular interest since D2 is the main target of antipsychotics.¹⁶

5-HT2A is proposed to be involved in the unique therapeutic action of clozapine.¹⁷ Two studies with sufficient statistical power have demonstrated a role for the structural 5-HT2A His452Tyr polymorphism in predicting clozapine response.^{18,19} Significant associations have also been described in at least a dozen other genes, such as *DRD3*, *DRD4*, *5-HT1A*, *5-HT2C*, *5-HT6*, *5-HTT*, *BDNF*, *COMT*, *GNB3*, *MDR1*, *MTHFR*, *NEF3*, *NRG1*, *RGS4* and *TNF-alpha*.^{2,20,21}

Of note, the first whole genome-wide association study of antipsychotic drug response was recently conducted by Sullivan et al.²¹ This approach involves no a priori hypotheses of candidate genes or gene variants, and as a result makes it difficult to interpret the significance of results in the context of adequately controlling for multiple variable testing. No significant findings have been reported thus far.

Also of note, only a few studies have tested for a direct association between CYP450 gene polymorphisms and drug response. These have yielded mostly negative results.^{2,22}

Overall, some interesting findings exist in the area of genetics and antipsychotic response. However, many associations are not conclusive and represent a small fraction of the total variance of treatment outcome. Because the entire genome and candidate gene variability have not been fully explored, more robust observations are expected with the utilization of DNA sequencing techniques. The category "treatment response" may

be too broad an outcome measure in genetic studies of heterogeneous conditions. Studies that target specific symptoms, such as neurocognitive and verbal memory scores, may yield more convincing findings.^{21,23}

Genetics of antipsychotic-induced side effects

Antipsychotics can induce a variety of side effects, such as involuntary movements (eg, tardive dyskinesia) and weight gain, both of which appear to be genetically determined.^{24,25} Compared with phenotypes like treatment response, an analysis of genetic factors associated with side effects may offer several advantages. First, side effects are often more closely related to plasma levels, which can sometimes be predicted by gene variants involved in drug metabolism. Second, compared with treatment response the occurrence of side effects may be more closely related to specific pharmacodynamic relevant receptors. Third, some side effects such as weight gain can be assessed more easily and reliably as compared with complex phenotypes, such as treatment response.

In a prototypical study of its time, Pollock et al²⁶ prospectively distinguished poor P450 2D6 metabolizers from EM among a group of elderly patients suffering from dementia treated with perphenazine. The poor metabolizers had significantly greater side effects than the 40 extensive metabolizers.

In the case of tardive dyskinesia, previous reports have indicated that CYP1A2 may be of importance.²⁷ Other studies which focused on the Ser9Gly variant of the DRD3 gene reported significant associations, which were supported in two meta-analyses.^{28,29}

Several interesting studies have now been published regarding the genetics of antipsychotic-induced weight gain. The CYP2D6 gene has been associated with increasing weight. In pharmacodynamic analyses, the most consistent findings involve the promoter polymorphisms of the 5-HT2C gene and the leptin gene. Both genes are involved in energy and fat metabolism in studies of humans and animals (reviewed in ref 30, *Figure 2*). Further interesting findings are reported in the ADRA2A and SNAP-25 genes, with replications in independent samples.³¹⁻³⁵

In summary, studies assessing the genetic underpinnings of side effects to antipsychotic medications have yielded interesting findings, although effect sizes for single genes (or gene variants) are small.

Genetics of antidepressant response and drug metabolism in depression

Major depressive disorder (MDD) is one of the fourth major causes of disability worldwide, with tremendous socioeconomic consequences³⁶ Adverse early life events are major predictors of later development of MDD, though genetic factors also appear to have a significant

influence (37% heritability in twin studies). Antidepressants are the cornerstone in treating depression; however, only 50% to 70% of the patients respond to initial therapy, and less than 40% patients achieve full remission.³⁷ Furthermore, efficacy of an antidepressant is often only apparent after treating for 4 to 8 weeks. A reliable tool to predict antidepressant response would be of great service to the clinician, leading to greater efficacy

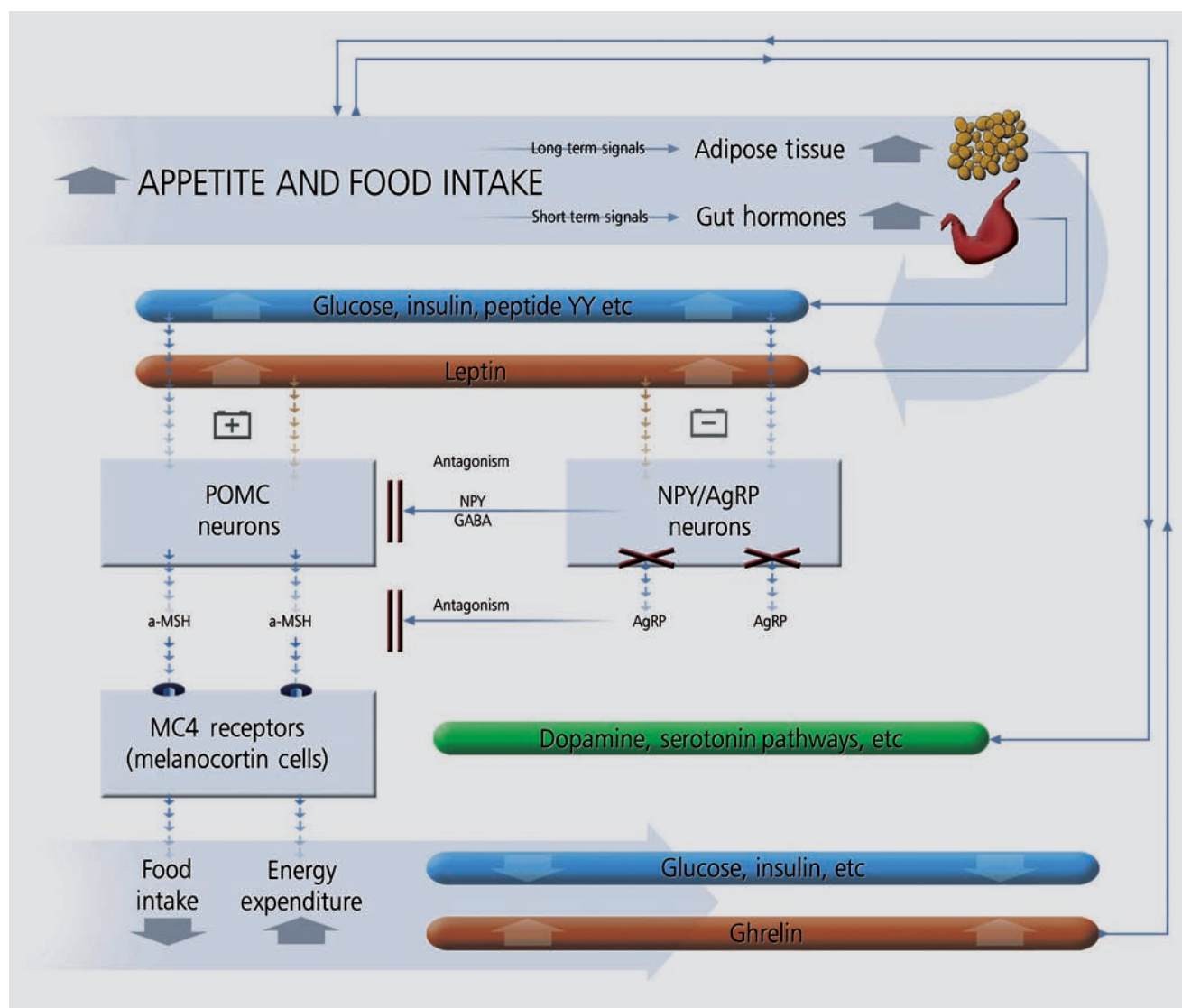


Figure 2. The interaction between peripheral molecules and central pathways modulating food/energy intake. AgRP, Agouti related protein, GABA, gamma aminobutyric acid, MC4, melanocortin receptor 4, NPY, neuropeptide, POMC, proopiomelanocortin, α -MSH, alpha melanocyte stimulating hormone. (source: www.silvermedia.ca)
Adapted from ref 30: Muller DJ, Kennedy JL. Genetics of antipsychotic treatment emergent weight gain in schizophrenia. *Pharmacogenomics*. 2006;7:863-887. Copyright © Future Medicine Ltd, 2006.

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and rapidity of response. Pharmacogenetics offers an individually tailored alternative to the trial and error prescription regime. Concordance for antidepressant response has been observed in family studies implicating the role of genetic factors.^{38,39}

Genetics of antidepressant drug metabolism

The therapeutic level achieved by antidepressants is heavily influenced by the metabolic activity of the CYP450 enzymes. CYP2D6 is involved in the metabolism of most tricyclic antidepressants (TCAs) and some SSRIs. Functional polymorphisms lead to varying degrees of metabolic activity that influence plasma drug levels, and allow for the categorization of distinct phenotypes (see *Genetics of antipsychotic drug metabolism* section above).^{6,40,41} The UM phenotype is associated with increased clearance of antidepressants and lack of response.⁴²⁻⁴⁴ Accordingly, the PM phenotype is reported to lead to increased adverse events with antidepressant treatment.^{45,46}

Some evidence suggests that functional polymorphisms in the CYP2C19 gene also influence serum levels of antidepressants metabolized by this enzyme. UM (CYP2C19*17/*17) exhibited the lowest concentrations of escitalopram, whereas patients with the PM genotype (CYP2C19*2 or *3) exhibited the highest serum levels.⁴⁷

Genetics of antidepressant treatment response

The selection of candidate genes for investigation is based on the hypothesized association with pharmacological targets of antidepressants. The ability of earlier antidepressants to increase the availability of monoamines within the synapse by either blocking monoamine reuptake (eg, imipramine) or inhibiting monoamine oxidase (eg, iproniazid) led to the monoamine-deficiency hypothesis of depression. As a result, several genes from the monoaminergic systems (eg, serotonin, noradrenaline, and dopamine receptors and transporters) have been investigated for their association with response to antidepressant treatment.⁴⁸

Among these, the serotonergic system is the most widely investigated. Genetic variation within the serotonin transporter (5-Hydroxytryptamin transporter, 5-HTT; SLC6A4) is suspected of conferring a vulnerability to anxiety and affective disorders. 5-HTT is the principal site of initial action for several antidepressants,

including selective serotonin reuptake inhibitors (SSRIs).⁴⁹ Polymorphisms within the promoter region were described shortly after the original isolation of the SLC6A4 cDNA on chromosome 17q12 by Lesch et al.⁵⁰ In particular, a site approximately 1200 bp 5' of the first exon of the SLC6A4 gene involves a 22 bp repetitive sequence consisting of two subtypes, a short (S) allele with 14 copies and a long (L) allele with 16 copies.⁵¹ This variation is frequently referred to as the serotonin transporter-linked polymorphic region (5-HTTLPR). The S allele is associated with a reduction of function as compared with the L allele. Cells homozygous for the L variant can have up to 66% more 5-HTT mRNA expression, greater serotonin transporter density in platelet and neuron cell membranes, and two times the serotonin uptake than cells with the S/S genotype (*Figure 3*).⁵²⁻⁵⁷

The L variant is generally associated with a better antidepressant response in Caucasian patients.⁵⁸ In a meta-analysis by Serretti et al, L carriers had better response and remission rates within 4 weeks of antidepressant treatment when compared with subjects with the SS genotype. Conversely, in an investigation of the STAR*D sample treated with citalopram (total n=1659) no association was observed between the 5-HTTLPR polymorphism and treatment tolerance or outcome.⁵⁹ In another analysis of the STAR*D sample a significant association was found between the L allele and remission in white nonhispanic patients.⁶⁰

Recently, the Genome Based Therapeutic Drugs for Depression (GENDEP) study⁶¹ found that the L allele was associated with better response to escitalopram. A significant interaction was identified between 5-HTTLPR, drug and gender, with the effect concentrated in males. Of note, the single nucleotide polymorphism (SNP) rs2020933, found at the 5' end of the 5-HTTLPR gene, also influenced treatment outcome in this study.

A common A>G functional polymorphism within the L allele has also been identified.⁵¹ The G variant of this polymorphism (LG) shows transcription levels similar to the S allele, whereas the A genotype (LA) shows higher expression levels. In the STAR*D study they reported a significant association between the LA allele and reduced adverse events in the white nonhispanic population, but not with treatment outcome.⁵⁹

The influence of 5-HTTLPR on antidepressant response is quite robust to ethnic differences although significant

heterogeneity exists in Asian samples.⁶² In contrast to Caucasian subjects, Asians carrying the S allele have been reported to respond better to antidepressants, although findings are mixed (see refs 37, 58, 63). Another gene of active investigation is *HT2RA*, which codes for the 5-HT_{2A} receptor, a target of both antidepressant medications and second-generation antipsychotics. A polymorphism rs7997012 found in the second intron was significantly associated with citalopram response in the STAR*D study.⁶⁴ In addition to this variant, the A1438G polymorphism also showed evidence of association with treatment outcome. Participants who

were homozygous for the A allele had an 18% absolute risk reduction of having no treatment response compared with those homozygous for the G allele. This finding appeared specific to white subjects. Conversely, the GENDEP study⁶¹ failed to replicate this association with rs7997012, and found that the G allele of another polymorphism, rs9316233, was associated with escitalopram response. Inconsistent findings have also been reported for the C allele of the T102C polymorphism.⁵⁸ Despite the lack of consistent findings for a specific polymorphism moderating response, the HT_{2A} gene as a whole appears to be of importance in depression outcome.

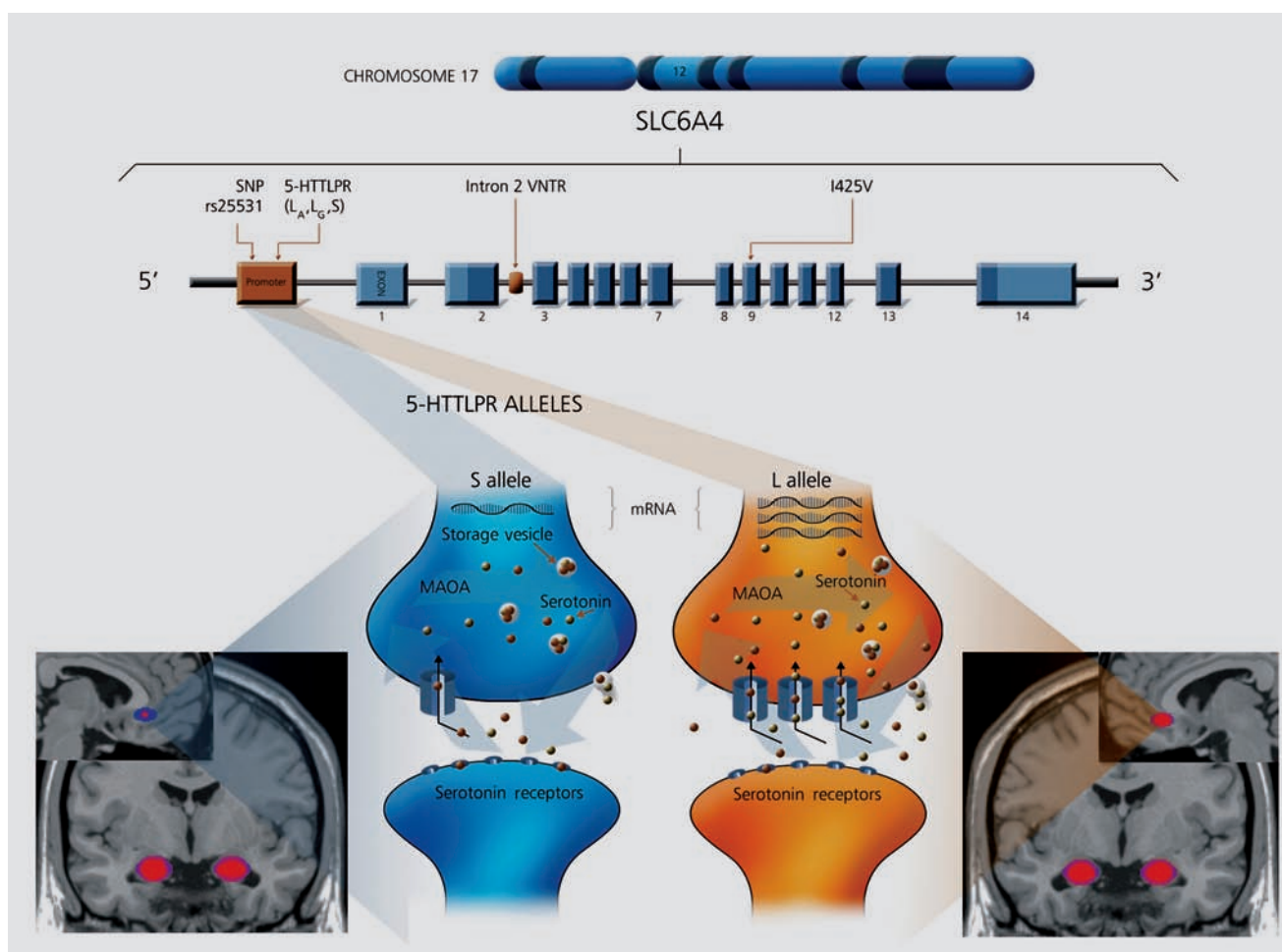


Figure 3. Serotonin transporter gene (SLC6A4) and function. *5-HTTLPR x PFC/Amygdala endophenotype interaction*. Allelic variation of the serotonin transporter (5-HTT), including the serotonin-transporter-gene-linked polymorphic region (5-HTTLPR), the variable number of tandem repeats (Intron 2 VNTR), rs25531 single nucleotide polymorphism (SNP), and the missense variant Ile425Val (I425V). The long (L) allele (orange) of 5-HTTLPR produces significantly less 5-HTT mRNA and protein expression, than the short (S) allele (blue), leading to higher concentrations of serotonin in the synaptic cleft. 5-HTTLPR s allele carriers show significantly less functional coupling between the amygdala and perigenual anterior cingulate cortex than L/L individuals. MAOA, monoamine oxidase A. (source: www.silvermedia.ca)

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Many other genes associated with the different monoaminergic systems that are either inconsistently associated with antidepressant response or that have produced contradictory results are reviewed in detail elsewhere (see refs 58, 63). These include *HTR1A*, *TPH1*, *TPH2*, *MAOA*, *MAOB*, *COMT*, *DAT1*, *SLC6A3*, *D2*, *D3*, *D4*, *NET1*, *SLC6A2*, *ADRA2A*, *ADRB1*, *G protein*, *beta polypeptide 3*.

Brain-derived neurotrophic factor (BDNF) is an important peptide abundantly expressed in limbic structures. BDNF is critical for axonal growth, neuronal survival, and synaptic plasticity. The observations of stress-induced decrease in hippocampal BDNF levels and increase in BDNF-mediated signaling following chronic treatment with antidepressants suggest a possible role in depression and its treatment.^{48,65,66} However, inconsistent and region-specific effects have also been observed.⁴⁸ A functional coding SNP rs6265 causes a Valine to Methionine change at codon 66, which leads to impaired intracellular trafficking and secretion of the mature BDNF protein. Carriers of the Met allele have significantly lower hippocampal volume than subjects homozygous for the Val allele.⁶⁷ Although several studies have found an association between the Met allele and antidepressant response,^{63,68} the sample sizes were small, and the results have been inconsistent.⁶¹ In addition to the Val66Met allele, a polymorphism in the 5' untranslated region of the BDNF gene (rs61888800) was associated with antidepressant response in Mexican-American subjects.⁶⁹ This observation requires replication.

Early life stress and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis are also linked with depression treatment outcome.^{48,70} One of the important genes that has emerged from the HPA axis is FKBP5 (FK506 binding protein 51), a cochaperone of 90 kDa heat shock protein, which regulates glucocorticoid receptor sensitivity. Carriers of the TT genotype of rs1360780 polymorphism in intron 2 of FKBP5 were demonstrated to have a better treatment outcome than other genotypes.⁷¹ This observation was replicated in a separate sample in the same study, and in two other independent studies. Smaller investigations of Spanish and Korean populations failed to reproduce this association (see ref 72).

Genetics of antidepressant-induced side effects

Side effects of antidepressant treatment have emerged as important reasons for medication discontinuation and non-

compliance. The first-generation TCAs and monoamine oxidase inhibitors (MAOIs) were primarily associated with sedation, weight gain, and anticholinergic side effects, including dry mouth, blurred vision, cardiac effects, and death by overdose. The newer antidepressants, including SSRIs and SNRIs, have better and safer side-effect profiles, but tend to cause nausea, diarrhea, nervousness, agitation, insomnia, and sexual side effects.

Similar to studies of antidepressant response, the candidate genes extensively investigated in relation to antidepressant induced side effects are from the serotonergic system. The presence of the 5-HTTLPR L allele is generally associated with fewer treatment related side effects. Negative studies are also reported in the literature. A recent meta-analysis found the L allele conferred protection against antidepressant side effects for all antidepressants (OR 0.64),⁶³ the significance of which became more robust when analyzed with SSRI-induced side effects only. The same meta-analysis found that the presence of the -1438 G/G polymorphism of HTR2A increased the risk of antidepressant side effects (OR 1.91). Several other pharmacodynamic genes were investigated with contradictory results.⁶³

Although strongly related to drug plasma levels, few important discoveries have been made linking pharmacokinetic associated genes and antidepressant-induced side effects. CYP2D6 polymorphisms are reported to influence the emergence of TCA and MAOI side effects, but not the majority of the newer antidepressants (for details see ref 72). Thus, the clinical utility of pharmacokinetic genes predicting side effects remains limited. To date, the most promising observations of an association between genes and antidepressant side effects have come from the 5-HTTLPR polymorphism.

Personalized medicine and neuroimaging

A major barrier to progress in the study of complex diseases, such as schizophrenia and depression, is the heterogeneity arising from etiological and phenotypic diversity. A significant amount of neuroimaging research has been conducted to identify biomarkers or endophenotypes which may reduce the heterogeneity. Proximal markers are presumed to be less genetically complex than the clinical phenotype. The identification of intermediary phenomena and specific gene-endophenotype linkages may increase the individual variability explained by candidate genes. The validity of biomark-

ers and endophenotypes is contingent on their sensitivity and specificity for the disease in question.³⁷

In the next sections we present the most promising neuroimaging markers of treatment response in depression and schizophrenia.

Neuroimaging markers of antidepressant treatment outcome

Anterior cingulate cortex

The most commonly reported finding in neuroimaging studies of depression is that increased rostral anterior cingulate cortex (rACC) activity predicts later response to depression treatment, including antidepressants,⁷³⁻⁷⁵ CBT,⁷⁶ and sleep deprivation.⁷⁷ Structural MRI measurements of the ACC have also demonstrated an association with treatment response.⁷⁸ The ACC is implicated in numerous brain functions, likely due to its neuroanatomical position as a bridge between frontal cortical and subcortical structures.³⁷ The rACC, primarily Brodmann area 25, is consistently reported to be hyperactive in depressed treatment responders.⁷⁹ According to Mayberg et al's theory of depression, cortical-subcortical regulation shifts from the dorsolateral to the ventrolateral prefrontal cortex (PFC), which contributes to rACC hyperactivity.⁷⁵ It is this region that is a target of deep brain stimulation (DBS) studies of treatment-resistant depression.⁸⁰ In further support of this theory, two independent groups of researchers have identified increased pretreatment activity in rACC theta activity in responders using low-resolution electromagnetic tomography.^{81,82}

Functional neuroimaging studies during active task conditions can facilitate distinguishing responders from non-responders by targeting the neurocircuitry involved in depression.³⁷ The aim is to reduce unexplained background cerebral activity ("noise") present during the resting state, thereby increasing the signal-to-noise ratio. Common approaches involve comparing the brain regions activated during the presentation of affectively laden or sad facial expressions versus neutral or positive stimuli. In an fMRI study by Chen et al,⁷⁸ participants who displayed greater pretreatment activation within ACC in response to negative versus neutral stimuli displayed the greatest response to treatment.^{73,74,83} Other fMRI studies have also demonstrated a relationship between pretreatment ACC activity and treatment outcome.^{73,74}

Amygdala

Greater pretreatment amygdala activity is also associated with treatment response. Increased signal in the amygdala following the presentation of negative facial expressions is related to major depression severity^{84,85} and was demonstrated to predict improvement.⁸⁶ Normalization of amygdala reactivity to affective stimuli is consistently reported to occur with antidepressant treatment.^{74,87,88} The same study that reported an association between PFC activity and response to CBT found that heightened amygdala activity to negative words also predicted response.⁷⁶ Intriguingly, there is evidence to suggest that the variability in amygdala and PFC activity is moderated, in part, by the serotonin transporter gene *5-HTTLPR*.

5-HTTLPR x PFC/Amygdala endophenotype interaction

5-HTTLPR appears to have modulatory effect on emotion⁸⁹ via top-down cortico-amygdala regulation.¹ On the one hand, diminished cortical structure and function is associated with depression and anxiety. Results from functional brain imaging studies suggest that the S allele contributes to increased amygdala reactivity via direct anterior cingulate (ACC)-amygdala dysregulation,^{90,91} and indirect compensatory activation of the ventromedial prefrontal cortex (*Figure 3*).⁹¹ Consistent with these findings, the S allele was associated with peak gray-matter volume reductions in the subgenual ACC, a structure implicated in both depression and anxiety.⁹² This theory is substantiated by the dense serotonergic connections between the ACC and amygdala in comparison with the relatively few amygdala connections with the ventromedial PFC.⁹¹ On the other hand, the gain of function L allele had the opposite effect of the S variant on cortico-amygdala regulation.^{90,91} The LA/LA genotype confers a modest risk of OCD,⁵¹ which is associated with hyperfrontality, including increased ACC metabolic activity and gray matter volume.⁹³

Hippocampus

Lower hippocampal volume is associated with depression, frequency of episodes, and chronicity of illness.⁹⁴ Hippocampal volume loss, as measured with structural MRI, is also characteristic of late-life depression and may be independently influenced by the val66met

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BDNF (See section *Genetics of antidepressant drug response*) and 5-HTTLPR polymorphisms.

5-HTTLPR appears to influence the pathogenesis of depression depending on the age of onset.¹ The S allele was associated with reduced hippocampal volumes in elderly subjects with early-onset depression (ie, first episode 50 years or younger), while homozygosity for the L variant predicted smaller hippocampal volumes in depressed subjects with later onset.⁹⁵ By contrast, the L/L genotype appears to contribute to the relationship between late-onset depression and dementia. Reduced hippocampal volume in this context may represent the effects of subcortical ischemia in vascular cognitive impairment⁹⁶ or the prodromal symptoms of depression often seen in Alzheimer's dementia.⁹⁷

Although not consistently reported, some studies have shown that antidepressant treatment may prevent or even reverse hippocampal atrophy via neurogenesis.^{98,99} More research is required to determine the reliability of hippocampal atrophy as a predictor treatment response.³⁷

Other regions

White matter hyperintensities on structural MRI negatively predict treatment response in late-onset depression.^{100,101} Fewer white matter lesions are associated with remission and maintenance of remission in late-life depression with antidepressant treatment.¹⁰¹ White matter disease commonly results in varied neuropsychological deficits, primarily memory, executive, and language function,¹⁰² which are associated with poor response to antidepressants.³⁷

Although the 5-HT transporter is widely believed to be involved in the pathogenesis and treatment of depression, positron emission tomography (PET) studies have shown both increased and decreased binding potential of the 5-HT transporter in the context of depression. These mixed results may reflect inter-study variation of etiology or mood state leaving it as an unreliable biomarker at present.¹⁰³

Neuroimaging markers of antipsychotic treatment outcome

Neuroimaging findings predicting treatment response to antipsychotics are less robust than those for antidepressants. Both brain atrophy by various measures (eg, sulcal width, ventricle size, etc.) and rate of gray matter loss

are associated with poorer treatment outcome. Ventriculomegaly¹⁰⁴ and cortical¹⁰⁵ and cerebellar atrophy¹⁰⁶ were found to predict response. More recently, the extent of gray matter atrophy over time was a better predictor of outcome than baseline abnormalities.¹⁰⁷

Neurochemical (PET) imaging offers a minimally invasive means of exploring distinct properties and cerebral distribution of neurotransmitter systems in vivo through the binding of receptor specific radiotracers. Binding potential is a principal measure in PET imaging studies that reflects both the density of available neuroreceptors and the affinity of a radiotracer to a given receptor. PET studies of dopamine 2 receptor (D₂) binding potential have shown that greater than 60% occupancy is associated with increased likelihood of antipsychotic response, while greater than 80% robustly predicts EPS.¹⁰⁸ The clinical application of neurochemical PET imaging remains limited by cost and availability, and while it has been instrumental in the reduction of antipsychotic dosing over the past decade and predicting dosing of second-generation antipsychotic drugs, it has not been applicable to the individual patients due to high inter-subject variability. However, a recent line of investigation in older patients with schizophrenia has provided new evidence from neuroreceptor PET imaging that may have potential for bedside translation. These studies have suggested that measurable changes in receptor reserve with aging is associated with antipsychotic medication and that medicated older patients on a stable dose of risperidone maintain individually consistent levels of receptor occupancy, plasma concentration, and psychopathology, supporting the use of this technology in prospective studies.¹⁰⁹ Presuming medication adherence, PET imaging data may, in the future, be used to facilitate the determination if worsening symptomatology or side effects are either due to alterations in neurochemistry or drug failure. Theoretically, this could be performed with antidepressant radiotracers specific for the serotonin transporter as well.¹¹⁰

In the future, PET imaging in conjunction with genetic testing for CYP 450 metabolism may help define individually tailored antipsychotic dosing schedules. UM may require higher doses of an antipsychotic to achieve the desired receptor occupancy, beyond the upper limits of what is currently defined as the normal range. Conversely, PM may require typically subtherapeutic doses to avoid developing side effects, such as EPS.

Preliminary work directed towards age-specific dosing

of antipsychotics has shown that EPS occurs at 50% to 70% D₂ receptor occupancy in the elderly, which suggests treatment efficacy occurs at even lower receptor blockade (~40% to 50%).¹¹¹ In the same study, a very strong association was observed between D₂ receptor occupancy and antipsychotic plasma levels. Pending replication, these results raise the possibility of predicting individualized antipsychotic dosing. Using population pharmacokinetic methodology in conjunction with neuroreceptor PET data, our group is currently investigating the predictive validity of individualized antipsychotic dosing using widely available bedside measures including plasma drug levels, drug dose, demographic factors, and concomitant medications.¹¹²

Conclusion

Personalized medicine promises the development of individually designed treatments based on the integration of all clinically relevant information, including data derived from laboratory, genetic, and imaging investigations, etc. The identification of pharmacogenetic and neuroimaging biomarkers associated with side effects and treatment response are active areas of research in psychiatry. The question is, when will genetic testing and sophisticated functional neuroimaging studies be implemented in clinical practice? With regards to genetic testing, a relative timeline can already be given. Genetic tests for critical drug-metabolizing genes, such as CYP2D6 and CYP2C19, are already available and can provide clinically useful information, potentially improving response rates and safety for those individuals who are poor or rapid metabolizers.¹¹³ It remains uncertain whether widespread genotyping prior to the onset of treatment therapy can contribute substantially to therapeutic outcome. Challenges facing the field include phenotypic and etiological heterogeneity, technological limitations, and con-

temporary research approaches. It seems that genetic testing for side-effect prediction has the highest likelihood of being incorporated into clinical practice. Supporting this, a test for clozapine-induced agranulocytosis is now available with satisfying sensitivity and specificity.¹¹⁴ Computational models that include gene variants and other factors associated with antipsychotic-induced weight gain have yielded promising results.¹¹⁵ Tests related to treatment response may follow through the inclusion of more sophisticated genotyping techniques (eg, sequencing) and the analysis of refined endophenotypes, such as specific symptoms or symptom clusters. Future development of algorithm-based approaches requires the integration of additional genetic and nongenetic factors.

Neuroimaging research has produced encouraging associations between imaging endophenotypes and treatment outcome, such as the 5-HTTLPR x PFC/amygdala interaction. Nonetheless, these observations lack the positive and negative predictive value required to reliably distinguish responders from nonresponders to be used clinically. Based on current research, imaging markers explain a significant, but modest, portion of the total variance. More research is required with larger, less heterogeneous samples in conjunction with other markers, eg, genotyping and electrophysiological measures.

Most neuroscience research thus far involves the application of various theoretical approaches (ie, neuroimaging, genetics, neuropsychological, and physiological, etc) in isolation. The next step in the development of personalized medicine is the formation of standardized multimodal research models to better characterize markers of treatment response. Now is a time for optimism in the emerging ability of pharmacogenetics and neuroimaging to provide meaningful help to the physician in developing individually tailored treatments for complex, heterogeneous psychiatric disorders. □

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La intersección de la farmacología, las imágenes y la genética en el desarrollo de la medicina personalizada

Actualmente se cuenta con numerosos ensayos controlados, randomizados y meta-análisis para tomar decisiones clínicas; lo que nos coloca en riesgo de descartar opciones terapéuticas específicas para un subgrupo de pacientes o en forma individual debido a su fracaso en la demostración de eficacia en grandes poblaciones. En la medicina personalizada está emergiendo una nueva era que se focalizará en las diferencias individuales, las que no son evidentes fenomenológicamente. Hay mucha investigación orientada a identificar genes, endofenotipos y biomarcadores de enfermedad lo que facilitará el diagnóstico y la predicción de la evolución terapéutica. Estamos en el umbral de la capacidad de predecir la respuesta al tratamiento, fundamentalmente a través de la genética y de las neuroimágenes. En esta revisión se analizan los marcadores más prometedores de la respuesta terapéutica y de los efectos adversos, que están surgiendo desde la farmacogenética y de las neuroimágenes en la depresión y la esquizofrenia.

Croisement de la pharmacologie, de l'imagerie et de la génétique dans le développement de la médecine personnalisée

Nous nous appuyons actuellement sur de grandes études contrôlées randomisées et sur des métaanalyses pour prendre des décisions cliniques, ce qui risque d'écarter des options thérapeutiques spécifiques individuelles ou de sous-groupes à cause de leur incapacité à prouver leur efficacité dans la population toute entière. La médecine personnalisée, stratégie d'apparition récente, a pour objectif de se pencher sur des différences individuelles qui ne sont pas évidentes sur le plan phénoménologique. Afin de faciliter le diagnostic et de prévoir l'évolution des traitements, la recherche se dirige vers l'identification des gènes, des endophénotypes et des biomarqueurs de la maladie. Nous sommes sur le point de pouvoir prédire la réponse au traitement, en particulier grâce à la génétique et à la neuro-imagerie. Cet article se propose d'examiner les marqueurs les plus prometteurs de la réponse au traitement et des effets indésirables issus de la pharmacogénétique et de la neuro-imagerie dans la dépression et la schizophrénie.

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Policy perspectives on the emerging pathways of personalized medicine

Gregory J. Downing, DO, PhD



Remarkable advances in the fundamental knowledge about the biological basis of disease and technical advances in methods to assess genomic information have led the health care system to the threshold of personalized medicine. It is now feasible to consider strategic application of genomic information to guide patient management by being predictive, preemptive, and preventive, and enabling patient participation in medical decisions. Early evidence of this transition has some hallmarks of disruptive innovation to existing health care practices. Presented here is an examination of the changes underway to enable this new concept in health care in the United States, to improve precision and quality of care through innovations aimed at individualized approaches to medical decision making. A broad range of public policy positions will need to be considered for the health care delivery enterprise to accommodate the promise of this new science and technology for the benefit of patients.

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Dialogues Clin Neurosci. 2009;11:377-387.

Keywords: *personalized medicine; genome-wide association study; pharmacogenomics; health information technology; clinical decision support; in vitro diagnostic multivariate index assay; coverage with evidence development*

Simply stated, for personalized medicine to become a hallmark of mainstream modern medicine, the attributes of precision and meaningful improvement in quality of health care through technology and information management must be obvious and unequivocal. Throughout biomedical science, there has been much anticipation of the potential impact of genomic, molecular, and personalized medicine for health. The beginning of 21st-century biomedical research was heralded by the completion of the Human Genome Project, which gave a great deal of momentum to new capabilities of science and technology in the hands of medical practitioners and the public.

Across the spectrum of clinical neurosciences, many advances are clearly being made toward understanding the biological underpinning of disease. Applications of new technology platforms in research are widely seen in neurodegenerative disorders, neuropsychiatric conditions, addiction, and developmental disorders. While the impact of translation of these new research frontiers will likely take many years to be measured, pressing implications requiring important policy considerations are visible today.

Significant innovation and technological achievements lie at the heart of the rapid pace of accrual of scientific information to support personalized medicine. Dramatic decreases in cost and increases in analytical throughput have placed within reach the possibility of sequencing a

Author affiliations: Project Director, Personalized Health Care Initiative, Office of the Secretary, Department of Health and Human Services, Washington, DC, USA

Address for correspondence: Gregory J. Downing, Project Director, Personalized Health Care Initiative, Office of the Secretary, Department of Health and Human Services, Hubert H. Humphrey Building, Suite 445F.5, 200 Independence Avenue, SW, Washington, DC 20201, USA
(e-mail: gregory.downing@hhs.gov)

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person's entire genome for \$1000. Broad applications of genomic characterization of disease states in the pharmaceutical, biotechnology, and diagnostic research sectors have become mainstays of early- and late-stage therapeutic development. Despite the robust investments in discovery research technologies to exploit genomic variation of disease-related genes, personalized approaches to disease management have raised challenges for industry because of the potential segmentation effect on diminishing the potential marketable population for new medical products. Nevertheless, there remains strong interest among pharmaceutical and biotechnology developers for clinical strategies to employ diagnostic tests in combination with therapeutic interventions. Whether this "codevelopment" approach will be widely employed by industry to enhance clinical development strategies, or is engaged in the clinical practice regimen as a personalized medicine tool, is largely unknown. The pathway toward large-scale use of molecular diagnostics in managing therapy decisions has substantial obstacles and misaligned incentives that will require significant policy modifications before personalized medicine becomes commonplace in health care.¹ While today's view of the horizon for many aspects of clinical practice remains unclear, some disciplines of medicine, such as oncology, are rapidly adopting clinical genomic analysis and individualization of therapies. Some of the more relevant challenges are not the scientific validity of the use of genomic tools, but rather the capability to deploy and organize information in meaningful ways in clinical practice. In addition, it is important to recognize that all of the discovery research and technological advancement is occurring in a highly volatile climate of change in health care policy. Access to health care, public financing of health care services, moving away from fee-for-service reimbursement models, comparative effectiveness research, changing focus on preventive health services, looming financing challenges accompanying dramatic shifts in demographics of aging populations, and continued concerns regarding security and privacy of health information are all part of today's policy framework, representing a cauldron of change in health care.

In this overview, the policy perspective of the translation of genomic science into health care practice is examined under the moniker of personalized medicine. The focus through this lens addresses how advances in science, technology, and health care in the United States come

together while recognizing that global influences in all of these domains are increasingly relevant to the domestic picture. Currently, personalized medicine addresses two general advanced technology platforms; molecularly targeted therapeutics which are selective for a specific biological marker (biomarker—defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention²), and molecular diagnostics. The latter, relative to the neuroscience areas, can generally be considered to include genomic diagnostic tests, biobehavioral testing measures, and imaging technologies. While recognizing the value of the contribution of many advanced imaging technologies to drug discovery and development and clinical disease state assessment, this report is principally focused on genomic diagnostic technologies. Currently, three broad medical applications of these technologies are most frequently considered as personalized medicine approaches: to determine likelihood of clinical response with molecularly targeted agents, to determine polymorphisms likely to contribute to adverse events or subtherapeutic response to drugs, and to assess disease biomarkers as predeterminants for diseases and conditions, such as heart disease, neurodegenerative disorders, and cancer.

In 2006, the US Department of Health and Human Services (HHS) initiated a federal effort to coordinate and facilitate steps across the agencies to establish pathways to enable genomic and personalized medicine to enter health care. In recognizing potential obstacles that predictive, preventive, and pre-emptive approaches to health care may face, the Personalized Health Care Initiative was launched to avoid unnecessary delays and develop effective communication strategies for the intended use of these technologies in health care. The framework for this initiative was built on two fundamental tenets: that linkage of clinical and genomic information would yield insights into human health and disease, and that the information gained from this linkage would be used, and not misused, to benefit patients and consumers.³ Recently, HHS published a report that included an analysis of health systems changes that were being undertaken in various institutions and through collaborative projects.⁴ The report also looked at the need for changing roles of key stakeholders in successful transformation of services in health care, required to successfully implement personalized medicine practices.

These analyses featured some of the implementation issues associated with personalized medical care and some of the solutions to overcome them.

Definitions and context of personalized medicine

The use of the term “personalized medicine” in the literature predates the advances in clinical genomics that have advanced the biological understanding of differences between individuals. Applications of this terminology were often related to customized behavioral approaches to management of health conditions. Prior to the 1990s, the use of the term “personalized medicine” was used to imply that there were sociological, educational, and psychological bases for alternative approaches to patient management that led to more or less successful practices. In the late 1990s, somewhat simultaneously with the approaching completion of the Human Genome Project, more common usage of the term reflected genetic understanding for differences in pharmacotherapy, ie, pharmacogenomics. This also coincided with the market entry of several molecularly targeted therapies in oncology that used genetically based determinants for the development and subsequent clinical application of novel therapeutic agents. Trastuzumab (Herceptin®), a monoclonal antibody that serves as a treatment for breast cancer, has often been heralded as the first molecular therapy ascribed to personalized medical applications through the use of an assay to detect overexpression of the Her2 protein, thereby identifying patients who are most likely to respond.

Since then, there have been many interpretations and contexts applied to the term “personalized medicine.” For the purposes of this discussion, the definition used here will be based on one by Willard et al as “the delivery of health care in a manner that is informed by each person’s unique clinical information; genetic, genomic, and other molecular biological characteristics; and environmental influences. The goals of personalized medicine are to take advantage of a molecular understanding of disease, combined with other individual factors, to optimize preventive health care strategies while people are still well or at the earliest stages of disease.”⁵

Increasingly, consumer interactions with the health care system and engagement in proactive participation in agenda setting and decision making are being applied to new ends. The rise of advocacy organizations and their

involvement in therapeutic development, application of social networking enterprises for patient connectivity (ie, PatientsLikeMe), greater involvement of public members in policy development, and growing public influences on coverage and reimbursement policies add new context to patient advocacy. Greater public awareness and growing understanding of personal utilities afforded by information technology, genomic analysis-assisted disease risk assessment, and computer-assisted living devices all bring a broader context to this discussion, which is referred to here as personalized health care (as distinguished from medical context of diagnosis and interventions).⁶

While much of the emphasis in discussions about personalized medicine has been focused on medical technologies, aspects of information technology are becoming their equal in enabling individualization or mass customization of health care schemes. This is not unlike the disruptive innovation qualities that computers have had in other industries, and will likely lead to wide-ranging and equally disruptive change for the medical community.⁷ One key characteristic of change will be the blurring of the lines between the established medical community, the patient/consumer, and other community members “linked” by information systems. In the future, personalized health care will represent an amalgam of patient experiences that will be customized, interactive, less episodic in nature, and more of a continuum of care. There will be many challenges ahead, in order for this model to be accepted and demonstrated to provide a higher quality of care, greater understanding by patients of their condition and health care choices, and improved efficiency and effectiveness of health care practices.

Key catalysts on the pathways to personalized medicine

The pace at which discovery research in human genomics enters translational research may be a trajectory unlike past novel interventions. In looking at personalized medicine through the lens of clinically meaningful impact, it is worthwhile to provide a context for some of the forces at play in creating the foundation for personalized medicine.

Genomic sequencing and related analytic platform technologies

The establishment of the public domain as the key reference source for the Human Genome Project opened the

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door to discovery research that continues to pay dividends in advancing scientific frontiers. Additionally, the substantial investments in large-scale science included funding for technology platforms and their applications in the project itself. As a consequence, there was a surge in the development of sequencing technologies yielding remarkably higher throughput, dramatically reduced costs, and greatly enhanced analytic capabilities. Government-supported incentives for technology development created an economically feasible environment that has expanded genome-scale research capabilities from large sequencing centers to the laboratory bench, and now, virtual discovery research through computational analysis. These efforts were first engaged to sequence targeted regions of the genome, in order to understand polymorphisms in genes and their contribution to genetic disorders. The HapMap project, by building a widely diverse international public genome database, rapidly accelerated the capability to compare population-based genetic makeup, resulting in highly annotated databases of disease genes.⁸ Evolutionary aspects of genomic information for understanding biological diversity came in the form of sequencing projects of other species. These projects yielded tremendous public resources that enabled biological understanding to be gained in model organisms, leading to broader insights into human development and disease mechanisms.

Advances in genomic information were not based solely on high-throughput sequence analysis. The development of microarray technology enabled ease of use for performing hybridization analysis on virtually any laptop computer. A new basis for diagnostic tests has been provided by the vast amount of gene expression data now available through large-scale measurement of mRNA abundance. The platform greatly expanded the capabilities to include comparative analysis of specimens for gene expression and the volume of genomic data that could be generated in hours of experimental time. Coupled with the development of analytical software, scientists are now armed with an adaptable platform to evaluate polymorphisms, compare the effects of interventions on DNA analysis, and ultimately evaluate pharmacologic impact on gene expression. Over the past 5 years, gene expression profiling has become a commonly used quantitative method in molecular and systems biology. In a short period of time, this technique has also become a common translational research tool widely applied in clinical medical laboratories, particularly in oncology for assessment of tumor biomarkers.

Genomic analysis platforms have had dramatic impact on clinical research and therapeutic research and development, and spawned a broad range of molecular diagnostic assays and devices. Meanwhile, medical applications remain unclear, as the clinical experience and evidence is lacking for many potential uses. Pharmacogenomics is viewed by many as a discipline of clinical pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity. By doing so, pharmacogenomics provides a rational means to optimize drug therapy with respect to the patients' genotype, to ensure maximum efficacy with minimal adverse effects. This approach sets the stage for personalized medicine, in which drugs and drug combinations are optimized for each individual's unique genetic makeup. The clinical impact of this has been primarily recognized in the alteration of many drugs' biotransformation profiles as a result of polymorphisms that contribute to slow or rapid metabolism. These manifestations are relevant to a broad range of pharmaceuticals, leading to either subtherapeutic responses in the case of enhanced activity of drug metabolizing enzymes, or adverse events from toxicologic manifestations of slowed drug inactivation. These studies have led to implications by the US Food and Drug Administration (FDA) to notify prescribing clinicians that pharmacogenomic testing may be of value in dosing and therapeutic selection, in some cases. The FDA maintains a list of drugs with labeling requirements that under some circumstances require pharmacogenomic testing of subpopulations for polymorphisms before the drug is prescribed.^{9,10}

Analysis of pharmacogenomic data has become a substantial undertaking by the FDA. Among these steps in developing the translational science for the future, the FDA, together with the pharmaceutical industry and academic investigators, has established a voluntary data submission process to enable better understanding of the interaction of developmental therapies with genes and their clinical manifestations.¹¹ Arguably, the largest number of patients with potential clinical application of a pharmacogenetics test under consideration in medical practice today are those who will be prescribed the anticoagulant warfarin. Several polymorphisms lead to the abnormal metabolism of the drug, which has a narrow therapeutic index fraught with medical complications. Research continues on the clinical importance of routine

testing of the *Cytochrome P450 2C9* locus, which is involved in warfarin metabolism, and variants in *Vitamin K epoxide reductase (VKORC1)*. Several commonly used drugs for neurologic conditions have FDA labeling for pharmacogenomic implications. Carbamazepine-related Stevens Johnson syndrome has been linked to polymorphisms in the *HLA B* haplotype. Individuals carrying one or two *1502 alleles are advised to avoid carbamazepine. Labeling for pharmacogenetic assay consideration is also present for fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) metabolized by *Cytochrome P450 2D6*. Abnormal clinical response may occur due to aberrant drug metabolism, and genetic testing may yield useful information to aid in dosing parameters.¹² A commercially available microarray has been developed and FDA approved for use to assist in determining *Cytochrome P450* polymorphisms, and other clinical laboratory tests are used in a variety of settings for consideration in drug dosing.¹³

Nonpolymorphic genetic modifications are increasingly being applied to understand gene-environment interactions in diseases and clinical conditions. Further expansion of the capabilities of microarray technology has enabled genomic analysis at additional levels by measuring DNA methylation and histone modification.¹⁴ In addition, analysis of copy number is providing insight about genomic variation beyond nucleotide polymorphism, showing significance in the etiology of cancer, atherosclerotic heart disease, and complex neurological conditions such as Alzheimer's disease and schizophrenia.^{15,16} Although not as commonly applied in the clinical laboratory as expression profiling, these methods are showing promise in therapeutic research and development and translational research genomic analytical laboratories.

Clinically meaningful laboratory applications in the future will need to overcome significant barriers. Currently, there are not widely accepted methods and standards for performing genomic analysis using array platforms. There is also wide variation in the analytical and computational methods used in comparative genomic analysis. In addition, there is a paucity of standardized control biomaterials for use in analyses. Finally, all of these quantitative measures are highly sensitive to clinical specimen acquisition, preparation, and storage methods. Little comparative work on standards for controls and disease biospecimens has been done on establishing normal datasets for gene expression methods.

Recently, a summary of these issues was addressed through a guidance document issued by the Centers for Disease Control and Prevention (CDC).¹⁷ The lack of highly annotated and fully characterized biospecimens with longitudinal phenotypic and demographic information remains a significant barrier for all of translational research in personalized medicine, but is most notable in large-scale genomic analyses.¹⁸

The application of the various genomic technology platforms has led to transformative research in population genetics. Over the last several years, population-based research studies, such as the Framingham Heart Study, have enabled large-scale genomic analyses from clinical resources. Collectively, these genome-wide association studies (GWAS), have enabled cross-study analyses from publicly available databases known as dbGAP (database of genotype and phenotype).¹⁹ Over the past several years, hundreds of new GWAS results have yielded insights into multigene effects to a wide variety of human diseases and conditions. Many of these new mutations are identified in noncoding regions. Collectively, the discovery of these new associations is prompting more hypothesis generation about disease pathways than generating platforms for new diagnostics and therapeutics. These public resources are proving to be useful discovery resources for various disease areas, such as psychiatry, enabling consortia of investigators to use statistical analytic methods to map genetic architecture of common disorders.²⁰

Information technologies in health care and impact on personalized medicine

A key infrastructure needed to establish a medical practice environment for individualized decision making is a robust and facile information technology capability. The reasons for this are the dependency on key attributes about the patient's health status, detailed data needs for phenotypic characteristics, and the complexity of the types of analytical data and decision algorithms that will be used to support more precise, preferred, and predictive health outcomes for the patient.

Much of the advances in genomic research have been supported by computational studies that have enabled large databases to be assembled with highly contextualized data to develop associative information about the relation of genes and biology. While technological advances in capacity for sequencing analysis have

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exceeded the benchmark measure of computing power, Moore's Law, there is no doubt that this success has been largely tied to computational advances.

The transfer of this knowledge from the laboratory to the health care setting faces a steep climb to establish information management practices in the US. Improved clinical knowledge from research is highly dependent on recovering standardized, useful clinical information from medical practice. The delivery of knowledge in clinically useful formats to support decision-making processes is similarly critical. The information management needs to span these gaps is found in the electronic health information technology (health IT). The major components of a health IT system to support personalized medicine includes widely used electronic medical record systems and personal health records that consumers can use for recording their own health care information. A second component is a nationwide effort to enable health information exchange among health care providers and institutions that will enable portability of information to suit purposes on demand. A third element includes electronic decision support capabilities that engage medical records systems to facilitate evidence-based health care choices by the health care provider. Collectively, these are dependent on data standards that enable semantic and syntactic interoperability of data across health IT systems. As a health care enterprise, the US has a dearth of electronic information to support these needs, and it will take many years to achieve all of these steps to benefit all patients. The inability to connect information sources is a major contributor to the high costs of clinical research, particularly clinical trials. Despite escalating health care costs and substantial service inefficiencies in the US, there has been little incentive until recently to make capital investments in information systems for the inpatient and ambulatory care setting.

Today, less than 20% of all physicians use electronic health record systems, and far fewer have systems that provide decision support capabilities to aid personalized medicine. Some progress is being made on the requirement for electronic transmission of prescriptions from the health care provider to the pharmacy. Computerized physician order entry (CPOE) for ordering laboratory tests and other services has also been improving. As part of the American Recovery and Reinvestment Act of 2009, nearly \$20 billion will be invested in the next several years to build health IT capacity through network capabilities, support acquisition of electronic systems by

practice groups and health care institutions, and provide fiscal incentives for adoption and use of health IT systems.²¹

The ability to harness clinical information and use it for research applications will be crucial for personalized medicine to benefit from these national investments. Paramount for patients is the knowledge that their information will be handled securely, that their privacy in health matters will be protected, and that the confidentiality of this information is respected. Altogether, for personalized medical practice to flourish and provide meaningful value, a health information exchange system must be developed that enables information to be mobile, standards-based, and support evidence-based medical care practices. The yield from this will be greater use of health care provider resources, more precision and predictability in medical choices, and provision of patients with more information and choices to address their needs.

Public databases and data access

One of the key facets enabling the rapid entry of genomic information into clinical application is the policy framework that underpinned the dissemination of research information. The public aspects of federally funded research did not stop with the completion of the human genome project. While the early part of this decade led to the birth of commercial entities that build genomic databases, the avenues of public information resources continued to evolve. A series of policies led major science and medical journals to require submission of newly discovered gene sequences into GenBank. This process of openness continued with establishment of additional databases requiring transparency of research, enabling resources to be used for new discovery rather than replication of results. One of the key building blocks for establishing the base for personalized medicine and the rapid advances of genomic research was built on fundamental public access policies initiated in the 1990s. In 1996, free Internet access to the National Library of Medicine Medline holdings of scientific information rapidly accelerated the dissemination of new science. The National Center for Biological Information added immense public databases of genomic information, imaging repositories, and many other resources that support the translation of research into medical applications. Further advancing this is a policy implemented in 2008

requiring all NIH-funded scientific publications to be made publicly available within 12 months of publication.²² PubMed Central, an open-source digital information resource, was established in February 2000 and has been followed by additional open-source publication venues. The net yield of these public policy efforts was to make biological information more readily available and accelerate the application of discovery research into clinical and translational research. While it is difficult to quantify the impact of public policies on the openness of scientific information, the effects have been widespread. Lowering barriers to commercial sector technology development, increasing the diversity of scientific collaborations, and enabling global research collaborations through the open language of science have been important steps to accelerate the arrival of personalized medicine.

Taken together, the profound advances in informatics platforms, allowing large and complex data to be moved rapidly, coupled with computational capabilities for gleaming meaningful associations of biological systems, have been transformative. Policies promoting sharing and dissemination of information have had a similar impact on accelerating the pace of science.

Vocabulary standards

The Human Genome Project brought with it a key aspect of data standards guiding the vocabularies of genetic information. The requirement to use internationally accepted common data elements for gene nomenclature and reference sequence information has provided specificity and avoided (to a large degree) confusion about the meaning of scientific data. Structuring digital biology to conform to unified modeling language (UML) has enabled genomic information to be modeled across all domains of scientific application through genomic standards, which has aided in the translation to clinical application. Standard clinical nomenclature is now being widely accepted for genomic test information. Health Level 7 (HL7), Online Mendelian Inheritance in Man (OMIM), Logical Observation Identifiers Names and Codes (LOINC), and Systematized Nomenclature of Medicine (SNOMED) provide widely accepted standards for clinical definitions, including disease and condition terminology, laboratory test information, and other terms for health care practices. Highly annotated clinical reference repositories for standards have been developed including the National Cancer Institute

repository of data elements caDSR (cancer data standards registry and repository). The caDSR is a database and a set of Application Programming Interfaces (APIs) and tools used to create, edit, control, deploy, and find common data elements (CDEs) for metadata consumers and for UML model development.²³

Protection of civil rights regarding genetic information

On May 21, 2008, the US framework of civil rights was enhanced through the signing into law of the Genetic Information Non-discrimination Act of 2008 (GINA).²⁴ This legislation was long sought on behalf of public interest, as the absence of federal regulations to prohibit use of genetic test information in employment decisions and provision of health insurance benefits on the basis of inherited traits was a deterrent for individuals to participate in research studies. Together with the Health Insurance Portability and Accountability Act provisions (HIPAA), GINA generally prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or an individual's family for decisions regarding coverage, rates, or preexisting conditions. The law also prohibits employers from using genetic information for hiring, firing, or promotion decisions, and for any decision regarding terms of employment. Importantly, the statute provides definitions regarding the consideration of genetic test and its application under GINA.

Regulatory oversight of genetic testing

In the US, the proliferation of genetic tests has raised awareness about a dichotomy in the regulatory framework across technology platforms and the federal agencies that oversee them. Molecular diagnostics that are performed in a laboratory as a laboratory-developed test are overseen by federal regulations issued under the Clinical Laboratory Improvement Act of 1972 (CLIA) that addresses the analytical validity of the testing procedures. Analytical validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest. Examples of common tests of this type include cytogenetic studies, immunohistochemical analyses, and fluorescent in situ hybridization assays performed by clinical reference laboratories.

Molecular laboratory assays that are assembled and marketed as "kits" are medical products reviewed by the

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FDA for analytical validity and clinical validity. Clinical validity of a genetic test defines its ability to detect or predict the associated disorder or phenotypic presentation. In this scenario, kits such as the polymerase chain reaction assay can be used in a clinical setting that may be outside of the clinical reference laboratory. The FDA review of these assay kits is considered a medical product under regulations of devices. In recent years, there has been much discussion regarding the different pathways that genomic assays may be brought into the clinical market based on the oversight of laboratory tests. Much of this discussion has been centered on a subset of clinical tests known as in vitro diagnostic multivariate index assays (IVDMIA) that integrate the analysis of multiple genes on technology platforms, providing an index score as a result. The mathematical algorithms that reflect the integration of these various gene expressions or polymorphisms are based on clinical population studies that associate the interaction of various genes under different clinical scenarios. Today, IVDMIA are used in guiding treatment decisions in breast and colon cancer, and providing clinical guidance regarding likelihood of recurrence under various treatment regimens. These tests are performed in clinical reference laboratories and are not subject to FDA review. A draft guidance has been issued that proposes that manufacturers of IVDMIA obtain premarket approval. Recognizing that the potential for a large number of complex genetic tests will be coming into the clinical marketplace in the near future, the Secretary of Health and Human Services requested a review of the federal oversight of genetic tests. The Secretary's Advisory Committee on Genetics, Health, and Society issued a comprehensive report in April 2008 that highlighted the impediments to data supporting medical use of genetic tests and recommended steps to improve the oversight process.²⁵

Policy issues regarding clinical utility and medical benefit from the use of genetic tests

Beyond the regulatory review of medical products, the integration of personalized medicine technologies into clinical practice also requires coverage and reimbursement of costs of the tests by health care insurance providers and other organizations that pay for health care services. A centerpiece of these considerations is the evidence that supports genetic test information adding value to the medical care experience. The clinical utility

of a genetic test defines the elements that need to be considered when evaluating the risks and benefits associated with its introduction into routine practice. Overall, the framework for supporting coverage and reimbursement decisions for genetic tests has been hampered by the lack of substantive clinical data to demonstrate confirmed value for their use in health care. The lack of a clinical trial infrastructure for diagnostic assays, similar to that for drugs and biologics, has made demonstration of clinical utility and medical effectiveness difficult to demonstrate. For personalized medicine applications, economic issues play some part in the inability of small diagnostic companies or reference laboratories to perform randomized clinical trials to show benefit by the determination of medical intervention on the basis of treatment outcome.

One suggested framework for considering the composite evidentiary needs for genomic tests identifies important information needs for medical use.^{26,27} In 2004, the Centers for Disease Control and Prevention (CDC) initiated a program to systematically review the clinical evidence supporting applications of genetic tests. The program, known as the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) conducts systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in the transition from research to clinical and public health practice.²⁸ Through this program, CDC supports evidence evaluations through literature reviews. One of the first studies conducted involved the use of pharmacogenetic testing of *Cytochrome P450* polymorphisms in patients being prescribed SSRIs. The evidence review concluded, as it has for a variety of other genetic tests, that there was insufficient data to support routine use of genetic testing.²⁹ Multiple other studies have been conducted to examine other genetic tests and similar findings were noted. This pattern suggests that to fully integrate genetic testing practices into health care, substantially more clinical research is needed to demonstrate clinical utility.

Health care financing considerations about coverage and reimbursement of genomic tests

The Centers for Medicare and Medicaid Services (CMS) recently deliberated on the coverage and reimbursement of pharmacogenomic testing. Coverage decisions regarding new health technologies under Medicare can be han-

dled in two ways: local coverage decisions that are made by petitioning authorization by the sponsor to a regional Medicare contractor, or a national coverage decision that CMS itself coordinates through administrative processes. The latter was employed by CMS recently through the conduct of an evidence review for coverage consideration of pharmacogenomic testing of genes associated with the biotransformation of warfarin, a powerful anticoagulant. In May 2009, after extensive review, CMS made a decision that denied coverage for routine warfarin pharmacogenomic testing as their findings indicated that clinical utility had not been demonstrated. CMS went further to outline parameters for future studies that they would consider supporting under a “coverage with evidence development” process. This process allows for the reimbursement of tests if done as part of a randomized clinical trial where utility can be assessed. To date, the alignment of evidence needs for pharmacogenomic tests to meet clinical validity and utility have not been mapped sufficiently for clinical studies to meet the regulatory needs of FDA and CMS. Further work in advancing the application of pharmacogenomics in medical practice could benefit from most strategic alignment of evidence needs and resources to support these studies.

The perspective of personal utility of genomic information has opened a door for new business opportunities in consumer health services. In 2008, several new direct-to-consumer services were launched, providing relatively low-cost genomic analysis and interpretation capabilities to the public, without a physician order. 23andMe, Knome, deCODEme and Navigenics are among the companies offer comprehensive genomic analysis and interpretation to consumers via a Web-based linkage. These services provide health information to patients about various personal traits (including behavioral tendencies) and risk assessment probabilities. The genomic tests in these cases are performed in CLIA-certified laboratories but not FDA approved. Some controversy has arisen over the validity of these tests and the consistency of analysis across platforms and databases. Furthermore, there is concern that none of the genomic information provided is directly medically actionable. Other genetic testing services focused on specific genetic mutations and their associations to neurologic and psychiatric conditions using data developed from GWAS studies have arisen, including those predicting likelihood of autism spectrum disorders, and suicidal ideation related to

SSRIs. Due to the lack of substantive clinical trials showing evidence to support these claims and the potential to cause patient confusion about the interpretation of the results, these tests have largely been controversial.³⁰ Among the issues frequently mentioned about the consumer genomics services are the variation in reference data populations used by the different services accounting for different interpretations of risk for the same patient, oversight of the clinical laboratory measurements through CLIA, and transparency of the use of the consumer information by the service providers.

Federal Trade Commission authorities are also playing a role in assessing unscrupulous marketing tactics by some companies of tests with unsubstantiated claims of benefit. Despite the uncertainty, these trends indicate several factors. Some segments of the consumer base are interested in potential genetic risks and may use this information to guide lifestyle and behaviors in their own health care. Moreover, the interest in consumer genomic services demonstrates some level of consumer empowerment and self-determinism that now permeates other segments of health care through social networking and community engagement. How these early experiences in commercial sector genomic services relate to future applications is unclear. The likelihood is, however, that armed with risk information, consumers will seek more insights from health care providers to guide them in the use of this information. Most health care providers, however, are poorly equipped at the present time and access to medical genetic counselors is sparse, although provided by some of the current consumer services.

Conclusions

Overall, the impact of genomic technologies on the understanding of disease and environment interactions has been substantial. To translate these advances into health care as personalized medicine will require substantial innovation in a systems redesign yielding transformative changes in the values, priorities, and roles of all participants. Building on information policies in research, we can anticipate that personalized medicine, in the context of health care reform, will need to address some key areas. Molecular diagnostics, for example, are likely to be required to have higher levels of transparency of supporting data, and confirmatory evidence that meaningful therapeutic selection decisions can be made on the basis of the information they provide. Some

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important decisions will need to be addressed in establishing a clinical research framework for evidence development in testing the applications of molecular diagnostics. Achieving this will almost certainly require more collaborative interactions between public and private sectors.

The attributes of potential cost savings through the reduction of adverse events and avoidance of using therapeutics when patients will experience no benefit will need substantive clinical evidence to support coverage and reimbursement policies. Application of genomic analysis in risk determination and behavioral and preventive interventions requires substantially more research to achieve the most beneficial applications of scarce resources. Furthermore, there will likely be a greater role for government-sponsored or public-private collaborations to support prospective and comparative trials to evaluate the contributions of genomic-based

diagnostic tests. Improvements in cost accounting throughout health care will be required to demonstrate the evidence that supports early detection and prevention strategies yield relevant health outcome benefits. Efforts to identify key data needs to assess clinical utility and cost-effectiveness of molecular diagnostics overall will help refine innovation goals for clinical application of genomics, and provide innovators with more specific targets for their research and development investments. Finally, substantial needs exist for education and training of health care providers across many disciplines to understand the patient care objectives of personalized medicine. If the course of these developments is focused on patient care and quality improvement processes, the future contributions of personalized medicine to patient care will be substantial. □

Acknowledgements: Jessica Nadler, PhD and Constanze Coon, PhD contributed to manuscript preparation and editing.

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Perspectivas estratégicas en los nacientes caminos de la medicina personalizada

Los notables avances en el conocimiento fundamental acerca de las bases biológicas de la enfermedad y los avances técnicos en los métodos para evaluar la información genómica han conducido al sistema de asistencia sanitaria a las puertas de la medicina personalizada. Ahora es posible considerar la aplicación estratégica de la información genómica para que el manejo del paciente resulte predecible, prioritario y preventivo, y se permita la participación del paciente en las decisiones médicas. La evidencia inicial de esta transición tiene algunas características particulares en cuanto a que las innovaciones alteran las prácticas de la asistencia sanitaria existentes. Se presenta una evaluación de las modificaciones que están en proceso para permitir que este nuevo concepto de atención sanitaria en los Estados Unidos aumente la precisión y la calidad de la atención a través de innovaciones dirigidas a propuestas individualizadas para la toma de decisiones médicas. Será necesario considerar una amplia gama de posturas de políticas públicas para las empresas prestadoras de atención sanitaria para que ajusten las promesas de esta nueva ciencia y tecnología para el beneficio de los pacientes.

Perspectives stratégiques dans la voie de la médecine personnalisée

Des avancées notables dans les connaissances fondamentales des bases biologiques des maladies et des progrès techniques dans les méthodes d'évaluation de l'information génomique ont permis de faire évoluer le système de santé au seuil de la médecine personnalisée. Il est désormais possible d'utiliser des applications stratégiques de l'information génomique pour guider la prise en charge du patient, afin qu'elle soit prédictive, préemptive, et préventive, et qu'elle permette la participation de celui-ci aux décisions médicales. Cette transition s'est illustrée de manière précoce par des innovations qui tranchaient avec les pratiques soignantes existantes. Nous examinons ici les modifications nécessaires à l'émergence de ce nouveau concept de soins aux États-Unis afin d'améliorer la précision et la qualité des soins par des innovations visant à individualiser la prise de décision médicale. Adapter cette nouvelle science prometteuse et la technologie pour le bien des patients nécessitera d'envisager une grande variété de positions dans l'élaboration de la politique des pouvoirs publics au service de la santé.

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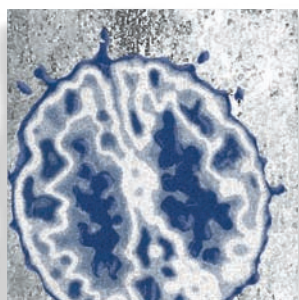
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Translational research

The role of neuroimaging in diagnosis and personalized medicine—current position and likely future directions

Michael Brammer, PhD



The main aim of this article is to discuss the current state of in vivo brain imaging methods in the context of the diagnosis and treatment of mental illness. The background to current practice is discussed, and the new methods introduced which may have the capacity to increase the relevance of magnetic resonance imaging, particularly functional magnetic resonance imaging, for clinical application. The main focus will be on magnetic resonance imaging, but many of the comments have a general relevance across imaging modalities.

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Dialogues Clin Neurosci. 2009;11:389-396.

Background: structural and functional brain imaging

A brain imaging method could be defined as any experimental technique that allows human (or animal) brain structure or function to be studied, preferably in vivo in the current context. Such a method should ideally produce accurate timing (in the case of functional imaging) and spatial localization (for both structural and functional imaging) of cerebral function, structure, or changes in these properties of the brain. The method should be minimally invasive and repeatable (to facilitate use in treatment monitoring and development of therapeutic strategies). Current structural magnetic resonance imaging (MRI) has good spatial resolution, is noninvasive, and meets the above criteria well for structural analysis. In contrast, no single technique currently in existence would meet all these criteria in the case of functional imaging, but the most common widely used methods are electroencephalography (EEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Of these three methods, EEG has been available for the longest time (but arguably not so as a viable mapping method). PET has been available for the second-longest period (in the order of four decades), and fMRI is the newest widely used technique. PET is arguably the most invasive (involving radioisotope administration) and EEG makes the closest approach to measuring neuronal activity directly (but has rather poor spatial mapping properties). As the location of cerebral activity and changes in activity associated with changes in brain state (either experimentally or illness-determined) seems to

Keywords: imaging; MRI; PET; brain; structure; function; analysis; diagnosis

Author affiliations: Centre for Neuroimaging Sciences, Institute of Psychiatry, Kings College, London, UK

Address for correspondence: Centre for Neuroimaging Sciences, Institute of Psychiatry, Kings College, Denmark Hill, London SE5 8AF, UK
(e-mail: m.brammer@iop.kcl.ac.uk)

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Selected abbreviations and acronyms

fMRI	<i>functional magnetic resonance imaging</i>
ROI	<i>region of interest</i>
sMRI	<i>structural magnetic resonance imaging</i>
SPM	<i>statistical parametric mapping</i>
SVM	<i>support vector machine</i>

have been the priority in most of the research to date, fMRI has emerged as the most widely used functional brain mapping method.

Structural MRI (sMRI) has been a common tool for the investigation of trauma and disease-related brain changes for some considerable time, but fMRI is a more recent addition to the MRI armory of methods. It has been available for a little less than two decades, since Ogawa et al¹ first coined the term BOLD (blood oxygen level-dependent) contrast for what has become the most widely used approach in use today. At first sight, BOLD imaging has a number of shortcomings. At what is still the most common field strength in MR scanners in clinical use (1.5 Tesla), the signal changes following neural activation are only a few percent. There are also a host of artifacts that can interfere with the signal, most notably head motion. The BOLD “signal” is also not a direct readout of neuronal electrical activity, but rather a downstream consequence of this activity, dependent on the response of the circulatory system. Finally, there is still a dispute about exactly what neural changes underlie the BOLD response (for a recent viewpoint on some of these issues, see Logothetis²). Despite all these apparent problems, BOLD fMRI has revolutionized the study of human brain activity. It is noninvasive (does not require administration of radioisotopes), can be performed repeatedly on the same individuals, and uses equipment that is increasingly widely available. There have been tens of thousands of papers published in which fMRI has been used to investigate a vast array of aspects of human brain function.

Brain imaging and psychiatry

When MRI technology first became available to psychiatry and neurology, one of the primary aims was to use this new technology to establish what have often been described as the “neural correlates” of various mental disorders, ie, to determine the location and magnitude of changes in brain structure or function compared with subjects from a suitable reference population. This would facil-

itate the identification of “biomarkers” (objective quantifiable changes in brain function) of the mental disorder in question. The longer-term aim was then to use these biomarkers to test the effects of drug treatment or behavioral therapy, ie, to use them as quantitative measures of the effectiveness of treatment in restoring “normality.”

As a research enterprise, the application of neuroimaging with the above aims has resulted in a very large number of studies and an impressive number of research publications in many of the major psychiatric and neuroscience journals, particularly in the case of fMRI. In 2003, barely a decade after the appearance of fMRI as a viable imaging tool, it was possible to list, in a book entitled *Neuroimaging in Psychiatry*³ produced by a number of my colleagues in London as well as eminent researchers from other centers, hundreds of research papers involving MR (as well as a large number from longer established methodologies such as PET). Since 2003 the knowledge base in this area has continued to expand at an impressive rate and, reading the literature to date, one might well conclude that fMRI has had a considerable impact on our understanding of abnormalities in brain function and structure. However, one might ask a different but no less important question. Standing as we do, almost two decades after the appearance of fMRI and having (as we do) access to widely available and reasonably reliable methods of analyzing brain imaging data, has brain imaging started to make an impact on the clinical issues of interest? Has brain imaging materially altered the pressing issues of the diagnosis and treatment of brain disorders?

This issue was the subject of a recent editorial in the *British Journal of Psychiatry* by Bullmore et al⁴: “Why psychiatry can’t afford to be neurophobic.” One of the issues raised in that article is “the reality of psychiatric practice in the UK, where there is currently agreed to be no clear role for neuroimaging, biomarkers or genetic testing.” The main question in relation to imaging is why the large number of research studies have not been translated into clear beneficial effects in clinical practice. This is clearly a complex and multifactorial issue, but the aim of the present contribution is to examine the simple question of whether neuroimaging is asking the appropriate questions of the data to maximize its relevance to psychiatry and drug discovery and development. For an interesting discussion of the general issue of using neuroimaging to understand brain function, see ref 5.

Background to current approaches to MRI analysis

In order to understand how the current approaches to MRI analysis have arisen, one needs to return to the period before fMRI was widely available, and brain activation and analysis was mainly undertaken using PET. The technique, known as region of interest (ROI) analysis, was the earliest to be employed and consisted, as its name suggests, of picking, *a priori*, a region or regions of the brain which were proposed, on the basis of previous findings or hypotheses to respond to the experimental task being studied. Typically, data would be averaged over the ROI(s) and the change in blood flow related to task performance would be studied, preferably with reference to a control (nonresponding) region or regions. This method remains arguably the simplest and one of the most statistically powerful approaches to studying changes in brain function and structure when the areas involved are well known or strongly predicted *a priori*. However, universal application of this method would entail a complete knowledge of all the brain regions involved in normal brain functions of interest, and (in psychiatry) when brain function or structure is abnormal. Given that we are still far from such a state of knowledge, more exploratory approaches were, and still are, needed in many cases. Ideally, these methods needed to be able to explore activity changes at the limit of resolution of the brain images (ie, at voxel level). In the late 1980s and early 1990s, Karl Friston and his colleagues at the Hammersmith hospital in London began to develop methods for the analysis of changes in brain activation over the whole brain, an endeavor which led to the development of the package known as statistical parametric mapping (SPM—for details see <http://www.fil.ion.ucl.ac.uk/spm/doc/#history>). This package, freely available to researchers since 1991, has become the most widely used approach for whole-brain analysis of functional imaging data. In order to achieve a principled approach to the problem, SPM developed a sophisticated way of dealing with the obviously severe multiple comparison problem inherent in performing tens of thousands of statistical tests, one at each voxel.⁶ This approach, using the statistical theory of Gaussian random fields,⁷ has earned Karl Friston deserved recognition for revolutionizing the analysis of brain imaging data. With the appearance of fMRI, the SPM package was rapidly adapted to deal with the rather different characteristics of the new data sets. Somewhat later, the possi-

bility of similarly analyzing structural changes voxel by voxel led to the development of what is now known as voxel-based morphometry or VBM. SPM was rapidly applied to large numbers of structural and functional brain imaging projects. It is the method of choice when changes need to be investigated over the whole brain, either because there is no strong prior hypothesis about the areas that need to be studied, or because the distributed nature of the expected changes makes ROI-based analysis very challenging. On a more prosaic note, it also removes much of the tedium (and potential error) of manually defining ROIs on large, high-resolution MRI data sets. Anyone who attempted to analyze structural MRI data prior to the appearance of VBM might speculate that the automated nature of this technique might have led many researchers to take this route, even when an ROI analysis might have been possible.

Since the early 1990s, there have been a large number of technical developments in understanding, and dealing with, sources of error in analyzing MRI data, and many excellent packages are now available, but the main analysis approach remains a suitably corrected voxel-by-voxel exploration of whole-brain activations (or structural changes) with inferences as to which brain locations are exhibiting significant effects or changes in effect brought about by the nature of the experimental task undertaken or the membership of a particular subject group (eg, patient/control). The main approach might be termed locationist and nonconnectionist, in that it seeks to locate areas of significant response (change) but ignores, by its independent voxel-by-voxel analyses, interactions between brain regions, at least at the primary phase of analysis. Note, however, that post-hoc connectivity analyses are often undertaken in the case of fMRI. Ignoring intervoxel interactions greatly simplifies the analysis, but ignores our current knowledge, suggesting that almost all significant brain activity involves network or system level behavior.

It is interesting to consider the pros and cons of this piecewise approach to the analysis of brain function on the current position of brain imaging vis à vis its uses in psychiatry and drug discovery and testing. The obviously positive aspects of 15 or so years of brain imaging research using (predominantly mass-univariate) fMRI are as follows. Firstly, our knowledge of the functional neuroanatomy of the brain has been expanded considerably. Secondly, if the multiple comparison problem inherent in mass univariate analysis has been tackled in

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a conservative and principled fashion, the areas that we have identified should be relatively robust, as the tendency would have been to make type II rather than type I errors. On the other hand, the lack of consideration of inter-regional interactions during whole-brain activation detection will mean that we have missed some activations that might be weak but highly correlated between brain regions. In other words, we might have under-reported and underdetected the distributed networks involved in many brain functions and in pathological changes in these functions. In simple terms, we have been “throwing away” useful information in the data sets during analysis. A more important consideration, central to the main theme of this article, is that, in the mass univariate analysis, there is no combination of information over the whole brain to assemble some sort of “figure of merit” indicating how well our analysis results allow us to, say, separate controls from patients, or drug responders from nonresponders. In other words, there is no indication of how well the whole-brain data would allow us to be confident that the pattern of activation was characteristic of a patient rather than a healthy subject. Instead of being able to make a prediction about an individual being healthy or not on a network-wide basis, we would instead be confined to making statements about the overall separation of groups at a particular voxel or in a particular region of interest, on the basis (typically) of a t statistic.

New developments in analyzing brain imaging data: machine learning methods

These observations on the mainstream fMRI analysis status quo have been made by a number of statisticians and neuroscientists in recent years.^{8,9} In response to the issues described above, growing interest has now come to be focused on a group of analysis techniques that have been described as “brain-reading” or “brain-decoding” methods¹⁰ that belong to a broad group of techniques known collectively as machine learning.¹¹ The basic idea of these methods is that, instead of analyzing the brain voxel by voxel, data from groups of voxels (ROI) or indeed from the whole brain, are used to train a computer program. In one set of classification methods, the most common variant of which is called the support vector machine (SVM), the program will typically find a boundary (referred to as a hyper-

plane in the relevant literature because it exists in high-dimensional space) between different classes of data (eg, data from patients and data from controls either from structural images of the same fMRI experiment). Once this boundary has been located, predictions can be made for data not in the training data set. For example, having trained the program to distinguish controls from depressed patients and define the optimal hyperplane to achieve this distinction, a new subject could be classified as belonging to the “patient” or the “control” class based on the relationship of their data to the hyperplane. The specificity and sensitivity of these predictions can be examined using standardized statistical approaches. In the most common of these, the so-called “leave one out” methods, the computer program is training on all the subjects but one and tested on the remaining individual. This is repeated until all the subjects have been the “one left out.” By averaging the results across all the tests it is possible to compute the sensitivity and specificity, where sensitivity here refers to the probability of correctly classifying a patient as a patient, and specificity the probability of correctly classifying a control as a control. If the data to be analyzed are obtained with a continuous rating (depression scores) rather than a classification variable (ill/not ill), then similar programs can operate on a data regression basis, learning the association between the continuous rating and brain structure or function. As well as providing information that may clearly be of value in a clinical setting in the form of classification accuracy, which communicates the level of confidence we can have in the predictions made by this type of analysis, these “brain-decoding” methods can also produce maps which indicate the levels to which different brain regions are involved in the classification accuracy that has been achieved. However, here a note of caution is in order. Unlike the maps produced by the more commonly used mass-univariate methods which can be unequivocally interpreted in terms of the size of the effect (eg, difference in response between groups) at each voxel, the maps produced by the machine learning methods explicitly contain the effects of interactions between voxels or brain regions. In other words, a particular voxel could be important in distinguishing two groups either because there is a large difference in function or structure at that point or because there is a small difference that is highly correlated with those in many

other brain regions, gaining importance from these correlations. There are two main consequences arising from this. The first is that the maps may be inherently more sensitive in depicting effects than those that we may be accustomed to seeing (though this is debated and is still undergoing detailed study). The second is that, unlike univariate maps, that can be subjected to statistical thresholding at a particular P value, thresholding these multivariate maps is more challenging, and the most effective way to accomplish this is an active area of investigation.

To summarize the above discussion, both the mass-univariate and multivariate “brain reading” methods of analyzing MRI data can give information about the location of disease-related changes in structure or function. The univariate methods are in fact easier to interpret, but may be less sensitive in detecting small changes to distributed systems. Few would argue, however, that if properly carried out, both approaches can potentially produce useful maps.

It is valuable at this point, however, to consider the relationship between producing a reliable map and establishing a usable biomarker for a psychiatric illness. The concept of a biomarker contains within it the idea of classification. It associates a pattern of changes in brain structure or function with a particular mental state. This is in fact the core idea of the “brain-reading” methodologies, as stated above. However, without knowledge of the classification accuracy associated with the map of brain changes, the map itself has little value. In a distinction between two classes, a random allocation process would produce a classification accuracy of 50%. A useful biomarker would be a pattern of changes with a classification accuracy of such a level that its probability of arising by chance would be very small. We can carry out such a test very easily. Having determined the classification accuracy as described earlier, we randomly allocate the data to the two classes of interest (thus achieving the null hypothesis of no difference between the classes) and repeat the “leave one out” testing. If we do this a very large number of times, we can establish how likely the classification process is to produce the original classification accuracy under the null hypothesis of no difference between the classes. In simple terms, we can see how far away from chance the classification lies. The further this is, the “cleaner” the separation between the groups achieved by the imaging “biomarker.”

Machine learning in current image analysis—a change of emphasis?

Although “brain reading” using machine learning methods (often also referred to as pattern classification methods) is currently arousing a good deal of interest, their use in the investigation of brain imaging is not new. In fact, they were used as long ago as the 1990s to investigate PET data.^{12,13} However, functional and structural brain imaging research has produced a host of new and interesting analysis methods over the last two decades. The reasons why some methods become widely used whereas others do not is a topic of considerable interest. O'Toole and colleagues⁸ devoted considerable space to discussing this issue and raised issues of what will move researchers out of their “comfort zone” to a new and potentially useful way of using their data. Given the availability of high-quality packages such as SPM, where mass-univariate analysis is efficiently implemented, and which are well-known and respected by neuroimagers, new methods have to be easy to use and to offer considerable added value to justify the investment in using them.

Why then does the author of the current article believe that machine learning methods may be widely taken up when many other promising methods have not? In the early 2000s considerable interest in questions of face/object recognition in the visual cortex led to some fascinating experiments. Notably, a very elegant study of face and object processing in the visual cortex by Haxby and his colleagues appeared.¹⁴ This paper did not use machine learning methods, but introduced the idea of associating brain states (recognition of different types of object) with distributed patterns of brain activity. Shortly afterwards, in 2002, Golland et al wrote a highly interesting account of the use of classifiers in brain imaging,¹⁵ introducing the use of the SVM, and in 2003 Cox and Savoy¹⁰ used an SVM (see above) in the same area of research as Haxby.¹⁴ It was clear from these data that information might be available in distributed patterns of brain activity that were not accessible by considering each voxel in isolation. Moreover, this information could aid classification. This was a way, not simply of locating functional or structural changes in the brain due to illness or a change in an experimental paradigm, but of using data from many voxels to explicitly classify brain data according to the group to which they belonged. A number of groups then began to realize that these ideas were

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much closer to the notion of a network-level biomarker than a statistically unconnected set of results from independently analyzed brain regions. Machine learning methods were soon applied to analysis of fMRI data,^{16,17} demonstrating the power to achieve good classification accuracies based on networks located in believable brain regions. It is but a small step from this point to the idea of automated diagnosis. In the area of structural MRI,

Alzheimer's disease has been one of the major targets for this latest phase of applications of machine learning.^{18,19} This is perhaps understandable, given that it gives rise to both distributed and major effects on gray matter density, making it an obvious target for a multivariate classification method. The use of fMRI for diagnostic purposes has also been investigated using SVM.^{20,21} Machine-learning based classifiers are currently achieving accuracies of

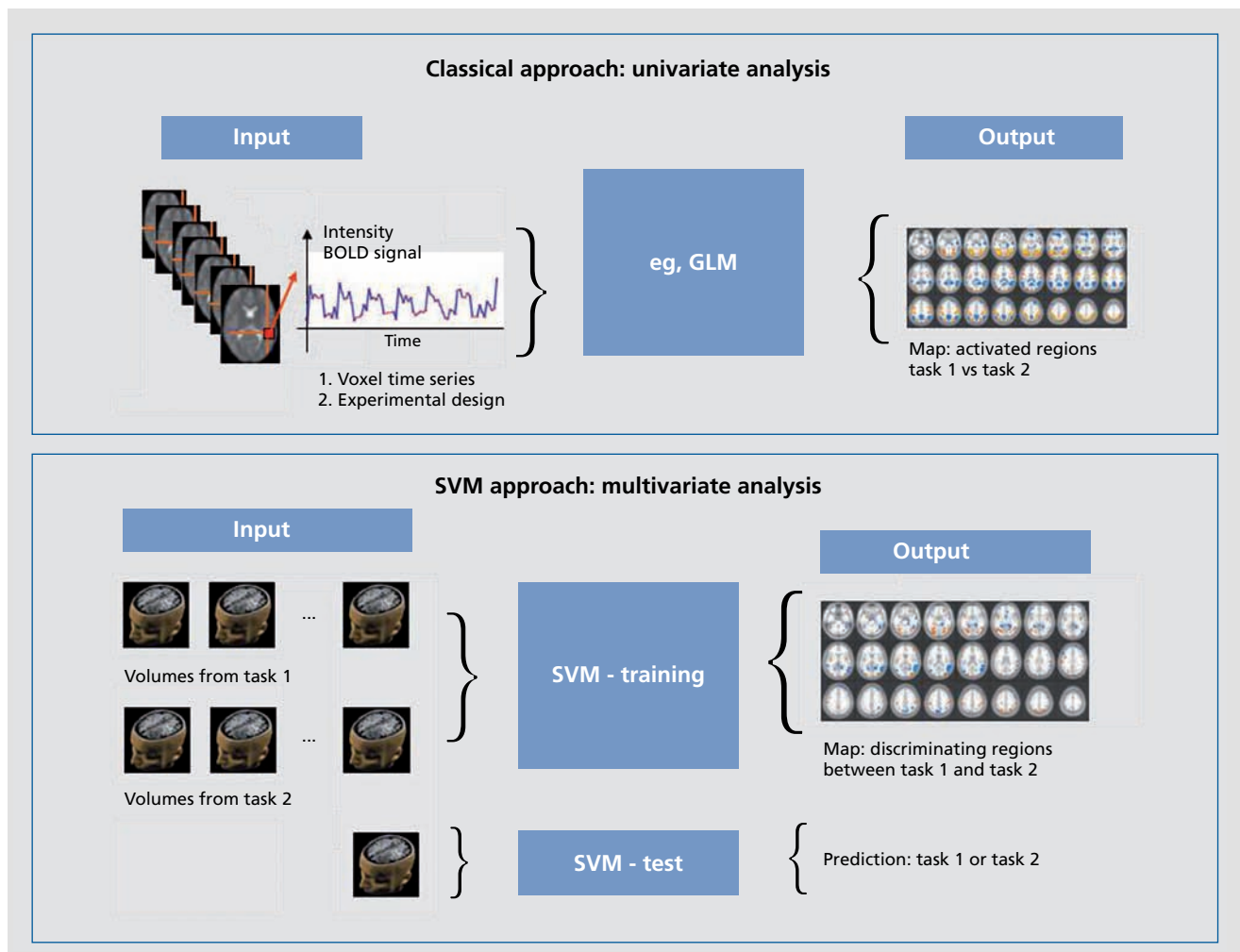


Figure 1. Data flow in a simple 2-task functional magnetic resonance imaging (fMRI) experiment (alternating blocks of each task) through traditional univariate analysis with general linear modeling (GLM) and support vector machine (SVM) analysis. The univariate approach analyses individual voxels using time points when task 1 is being performed and time points where task 2 is being performed, contrasting the two using a simple statistical test (eg, a t test) with a correction for the number of voxels analyzed. The output is a map of regions where the responses to the two tasks are significantly different. SVM-based analysis takes whole-brain volumes when task 1 is being performed and whole-brain volumes when task 2 is being performed and “trains” a computer program to associate patterns of fMRI response with each task. The outputs are a map of the regions which discriminate between the two tasks and a measure of how well the two tasks are discriminated on the basis of the whole brain data. After training, the task being performed can be predicted purely from the fMRI data. For group separation, tasks 1 and 2 can be replaced by groups 1 and 2 (eg, patients/controls) performing a given task or structural MRI data from the two groups.

75% to 95% using functional and structural imaging data and active research in this area is extending the armory of methods beyond categorical classification to probabilistic output using techniques such as Gaussian Process methods.²² Other techniques of interest include single-class SVM in which the goal is outlier or novelty detection. This method has considerable promise for detection of deviations from statistical homogeneity in clinical populations.

In a recent demonstration of the possibilities for machine learning, Sato and his colleagues carried out an interesting experiment.²³ They first trained a computer program (using a technique called maximum entropy linear discriminant analysis) to recognize the association between age and brain activation changes during performance of a motor (finger-tapping task). They were then able to predict the ages of subjects not included in the training purely from their brain activation data. If one imagines the association computed in this experiment as a biomarker for age, and then extends the logic to other areas (eg, changes in depression) one can appreciate the possibilities of the method.

Some of the most exciting possibilities of machine learning methods in clinical practice stem from the ideas raised in the two previous paragraphs. One is that we may be able to locate individual patients on a continuum of brain structural or functional abnormalities that are correlated with illness severity. This would be a great advance on simply categorizing an individual as belonging to the group of “controls” or the group of “patients.”

We would also be able to identify patients who, on the basis of their brain structure or function, appeared to be atypical of their diagnostic group. The second is that this “continuum” or probabilistic rather than categorical approach, could be extended from diagnosis to response prediction—personalization of treatment. The probability that a given patient might be a “responder” rather than a “nonresponder” based on objective measurement of brain structure or function would be a valuable adjunct to the choice and direction of treatment.

In order to make these new methods available on a wide basis, a number of groups are also actively developing toolboxes with user-friendly interfaces. Also, in order to avoid repetition of already time-consuming image processing, these toolboxes are often being designed to accept data from widely used preprocessing streams in packages such as SPM.

Conclusion

Seventeen years ago, it was felt that fMRI might revolutionize the study of human brain activity.^{1,24} Arguably, this has proved to be the case. It was also felt by many that fMRI might prove to be an invaluable clinical for the investigation and treatment of mental illness. There are many who would argue that has not proved to be the case. Kosslyn in 1999⁵ asked “If fMRI is the answer—what is the question?” With machine learning, perhaps fMRI may be able to answer more of the questions that we wish to ask. □

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El papel de las neuroimágenes en el diagnóstico y en la medicina personalizada: situación actual y probables proyecciones futuras

El objetivo principal de este artículo es analizar la situación actual de los métodos de neuroimágenes in vivo en el contexto del diagnóstico y del tratamiento de las enfermedades mentales. Se discute el fundamento de la práctica actual y los nuevos métodos introducidos, los que pueden tener la capacidad de aumentar la importancia de las imágenes de resonancia magnética, en especial de la resonancia funcional, para la aplicación clínica. El foco principal estará en las imágenes de resonancia magnética, pero muchos de los comentarios tienen una relevancia general para las distintas modalidades de imágenes.

Rôle de la neuro-imagerie dans le diagnostic et la médecine personnalisée: position actuelle et perspectives éventuelles

Cet article vise principalement à examiner la place actuelle des méthodes d'imagerie cérébrale in vivo dans le contexte du diagnostic et du traitement des maladies mentales : une discussion du cadre des pratiques actuelles est proposée, ainsi qu'une introduction aux nouvelles méthodes qui pourraient augmenter la pertinence de l'imagerie par résonance magnétique, plus particulièrement l'IRM fonctionnelle, en ce qui concerne ses applications cliniques. Le sujet principal en est l'IRM, mais un grand nombre des commentaires sont également valables pour d'autres méthodes d'imagerie.

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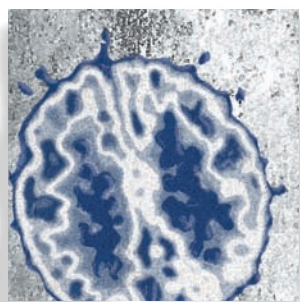
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Stem cell approaches in psychiatry—challenges and opportunities

Jens Benninghoff, MD



Exploring stem cells is a fascinating task, especially in a discipline where the use of stem cells seems far-fetched at first glance, as is the case in psychiatry. In this article we would like to provide a brief overview of the current situation in relation to the treatment of mental diseases. For reasons that we will explain, this review will focus on affective disorders. The following section will give a more detailed account of stem-cell biology, including current basic science approaches presenting in-vivo and in-vitro techniques. The final part will then look into future perspectives of using these stem cells to cure mental illnesses, and discuss the related challenges and opportunities.

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Dialogues Clin Neurosci. 2009;11:397–404.

Keywords: stem cell; neurogenesis; transplantation; depression; schizophrenia

Author affiliations: Department of Psychiatry, Ludwig-Maximilian University, Munich, Germany

Address for correspondence: Jens Benninghoff, MD, Molecular and Clinical Neurobiology, Department of Psychiatry, Nussbaumstrasse 7, D-80336 Munich, Germany
(e-mail: jens.benninghoff@med.uni-muenchen.de)

Regenerative medicine appears to be on the brink of a bonanza in terms of new treatment options, ie, stem cell-based therapy. Up to now, stem cell-based interventions (SCBI) have still been in an immature state. Only a few trials are currently under way, and are so far mostly in a preclinical phase. Current focuses include Duchenne's disease, Parkinson's disease, and Alzheimer's disease.¹ The major concept of all these experiments is to create a treatment scheme similar to that in bone-marrow diseases where hematopoietic stem cells are regularly used as a cure for certain types of leukemia—in this case, the issue of the appropriate stem cell type used has been solved. For SCBI in neurodegenerative disease there is an ongoing debate regarding which cell type might be suitable for transplantation—embryonic versus fetal versus adult stem cells. Furthermore, the question of stem-cell homing needs to be addressed, since one may not need to transplant the cells by neurosurgical procedures. Instead, it could be sufficient to inject these cells into the cubital vein only,² since the plasticity of these cells enables them to find the niche where they are needed—even within the central nervous system (CNS).

Apart from technical aspects, ethical problems arise. Even without touching on the debate of using human embryonic stem cells, there is plenty of groundwork for bioethicists to do.

When the ethical and technical issues have been resolved, we may proceed from neurodegenerative to psychiatric illnesses such as affective disorders and schizophrenia.

We still face a substantial lack of proof as to whether these psychoses are the cause or the correlate of disturbed adult neurogenesis.³ If so, we may consider these severe illnesses as being neurodegenerative, as there is some compelling data for this, at least in the field of

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Selected abbreviations and acronyms

5-HT	<i>serotonin</i>
BDNF	<i>brain-derived neurotrophic factor</i>
CREB	<i>cAMP response element binding protein</i>
ES cells	<i>embryonic stem cells</i>
SCBI	<i>stem cell-based interventions</i>

depression. There may be some clinical trials of grafting stem cells, in a long and cumbersome process, into the brains of diseased patients. In our opinion, this will only be the case for very severe cases of depression, after having tried nearly all the available medication options and unsuccessful electroconvulsive therapy (ECT).

Past and current status

In the past, psychiatric diseases have been treated pharmacologically with broad-profile medication—the so-called “shotgun method.” In the same way that a shotgun fires many pellets at once, psychiatric medication can impact on many different neurotransmitter systems. Due to this profile, many of these drugs, such as tricyclic antidepressants (TCAs) or first-generation antipsychotics (FGAs) caused severe undesirable side effects, which were held responsible for poor compliance and discontinuation of the prescribed medication.

During the last two decades, new drugs have surfaced with fewer shotgun side effects because of their particular pharmacodynamic design targeted against one single and very specific molecule. In this context, selective serotonin reuptake inhibitors (SSRIs) should be mentioned here as an example of an antidepressant agent acting solely on one neurotransmitter system and within the serotonergic system on one distinct transporter molecule. The same holds true for second-generation antipsychotics (SGAs) displaying only few side effects due to less rigid inactivation of dopamine receptor type 2 (DR2) and therefore fewer extrapyramidal motor symptoms recalling parkinsonism.

Nevertheless, we are still struggling with inefficacious medication, since only about one third of antidepressant agents work in a given patient, meaning that one has to try on average three different medications in order to alleviate this patient’s symptoms. For schizophrenia the same holds true. Sometimes, the individual situation seems even worse than in the field of affective disorders.

Some stem cell basics

As mentioned above, this article emphasizes the link between disturbed adult neurogenesis (AN) and affective disorder. The case seems to be much more evident here than in schizophrenia, although decreased neural stem cell proliferation in the dentate gyrus (DG) of the hippocampus has been demonstrated in postmortem human brain from schizophrenic patients.⁴

Stem cells can be characterized by two fundamental qualities: first, they have the capacity for unlimited self-renewal, and second, they can produce at least one type of highly differentiated descendants.⁵ This particular cell division is termed “asymmetrical”: in general, each stem cell division gives rise to one stem and one committed somatic daughter cell.⁶ Stem cells are single cells that, once developed, self-renew for the lifetime of the organism. These stem cells should be distinguished from transient progenitor cells, which have a limited self-renewal lifespan.⁷ Some steps earlier during the embryonic period, cells become gradually restricted to distinct pathways of differentiation. This process includes modification of their developmental potential; they become pluripotent (“many, several”). The major difference between totipotency and pluripotency is that an embryonic stem cell (ES cell) which is by definition “pluripotent,” can only form cells which constitute the embryo itself but not the placenta. Early ES cells can be taken from the embryo and grown in vitro. When retransferred into the embryo, these cells can still generate all tissues, including the germ line.⁸ ES cells also play a central role in the generation of transgenic animals such as knockout mice.

Pluripotency of stem cells becomes progressively restricted and they become multipotent. Multipotent stem cells in the brain ultimately give rise to all different types of neuronal and non-neuronal cells in the central nervous system. Presumably they have lost the ability to produce cells of ento- and mesodermal origin. Because they are capable of generating the entire progeny of a given tissue, some investigators have termed these multipotent stem cells “progenitor cells.” Moreover, there is controversy as to whether neural stem cells can actually remain viable during the entire lifespan.⁹

Adult forebrain neural stem cells were discovered in 1992¹⁰ in the adult remnant of the embryonic brain germinal zone surrounding the lateral ventricle. Evidence for their participation in repopulating the adult lateral ventricular subependyma following irradiation¹¹ led to the

hypothesis that neural stem cells also exist after the embryonic and fetal period, similarly to hematopoietic stem cells. Hematopoietic stem cells in adult animals can restore different blood cell types. For a long time it has been thought that once a cell had been programmed to produce a particular tissue, its fate was sealed and it could not reprogram itself to form another tissue. Contrarily to this view, reactivation of dormant genetic programs appears to work under certain circumstances. Intriguingly, stem cells from brains of adult mice have been shown to possess the potential to become functional blood cells.¹² Similar results for the inverse case were reported, ie, multipotential mesenchymal cells transformed into neural cells—astrocytes in this case.¹³

According to Fred H. Gage, the term “neural stem cell” should therefore be used with caution to describe cells that “a) generate neural tissue, b) are capable of self-renewal, and c) give rise to cells other than themselves through asymmetric cell division.”¹⁴ In fact, when the issue of lineage specificity of adult neural stem and progenitor cells is considered, there is abundant reason for caution regarding the term neural stem cell. The ability of bone marrow stem cells to generate astrocytes,¹³ the finding that astrocyte-like cells in the subependyma are neural stem cells,^{15,16} and that oligodendrocyte-precursors contribute neural stem cell-like cells¹⁷—all these findings soften the theoretical distinction between stem and progenitor cells. All this makes it really difficult to decide which type of stem cells one should use for transplantation. Even during the process of grafting stem cells they can still start to differentiate and become more restricted progenitors due to cell-cell contacts or influence of adhesion inside the syringe.

Further, neural stem cell research suffers dearly from the lack of an antibody specifically identifying neural stem cells. Detecting stem cells *ad hoc* and not *ex post* remains a problem. Putative stem cells need to differentiate into their derivative neural cell subpopulations before one can positively identify them as regular neural stem cells. In the past, efforts to generate antibodies against adult stem cells did not prove sustainability.^{18,19} There are certain advantages of adult over embryonic stem cells in that the former may be easier to manage. ES cells tend to differentiate spontaneously into all kinds of specified tissue. For example, when injected subcutaneously into immunocompromised mice they grow into teratomas, tumors consisting of numerous cell types ranging from gut to skin. Before applying these cells in humans, gen-

eration of the desired cell types should therefore be ensured without undesired side effects or unwanted cell populations, respectively. Here, it seems that adult stem cells are better behaved, since they do not differentiate spontaneously.

Instead this can be induced by applying appropriate growth factors. However, adult stem cells have a different drawback, in that they seem to lose their ability to divide and differentiate after some time in culture. Maybe in the end ethical considerations will also convince the scientific community to follow the adult stem cell rather than the ES cell track. Compared with embryonic or fetal stem cells, adult stem cells pose fewer ethical problems because they can be obtained from sources other than embryos or aborted fetuses.²⁰ Even post-mortem human tissue can yield neural stem cells.²¹ In consensus with Frank E. Young²² the public, as well as governmental authorities, should enter the process of unbiased dialogue, in order to establish the principles according to which research needs to be conducted.

As of now, we should consider the human species an appropriate source for SCBI. Having said this, we should take into account possible chimeras of animals with human cells in their brains, and above all with possible human behavior.²³ Another issue to be ruled out is to prevent striking behavioral traits after SCBI. In Parkinson's disease patients it has been shown that after L-Dopa treatment some patients responded with pathological gambling,²⁴ since dopamine sustains the reward system. One could easily imagine a scenario like this in a patient after SCBI. In this case, it might not be as easy to lower the dopamine production as it is with cessation of the medication.

As mentioned above, grafting hematopoietic stem cells has already become a conventional clinical tool in the treatment of certain types of leukemia. Currently it can only be hypothesized that transplantation of neural stem cells has potential for treating brain disease.²⁵

Although all these obstacles do exist, the main target for the research on neural stem cells must be to restore regular neural function in areas where cells have died or lost their physiologic behavior. Clinicians are eager, for example, to transplant NSCs into patients suffering from Parkinson's disease,²⁶ multiple sclerosis, or spinal cord injuries, although it is not clear so far which is the appropriate cell to transplant—the CNS neural stem cells, the actual neurons, or intermediate progenitors between the two. Thus, in neurodegenerative diseases it is important to first determine the rules of transplantation of stem,

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progenitor, and mature cells, as well as to determine the sites into which the transplants must be located. In Parkinson's disease we do not know whether cells should be placed into the substantia nigra, or striatum, or both. So we continue wondering which particular region of the abovementioned brain areas should be chosen—eg, the ventral part or the dorsal putamen in only one hemisphere or both. The variability in surgical methods between centers which perform stem cell transplantation makes it very difficult to assess the results of this procedure.²⁶ Still, if we get to the point where all these issues are resolved, we will have to find better ways to secure the long-term survival of the grafted cells.

So far, the *de novo* generated dopaminergic neurons have only a limited lifespan in animal studies.²⁷ Finally, the source of the cells should be clarified, since we need huge amounts of human fetal tissue for transplantation. Although there has been much progress achieved over the last few years, especially in long-term proliferation and dopaminergic differentiation of progenitor cells,²⁸ we still have to invest much effort in finding alternative methods, such as *in vivo* mobilization of dormant neural stem cells, which seems to be a more useful concept.

Pathophysiologic models of depression

In the light of recent findings such as loss of total cell volume in certain brain areas observed in depressed patients (see below), we can heretically define depression as a “neurodegenerative” disease. As we will discuss, this particular illness does not necessarily require stem cell transplantation. Instead, it may be possible to replenish missing neurons by regulating the microenvironment surrounding the putative sites of neural stem cells where neurogenesis takes place. Lessons from recent findings in pathophysiology might open up a broad research avenue with the ultimate goal of treating depression.

In a WHO survey, depression and manic-depressive illness will still rank among the top 10 causes for death in the year 2010. Certainly not all forms of depression eventually lead to death by suicide, but even milder courses of this illness may lead to severe incapacitation of millions of people worldwide. In particular, it impairs reintegration into their familiar social environment and into the working process. Accumulating evidence from neurobiology suggests that distinct biochemical processes are derailed in a large number of depressed subjects. Cellular and molecular adjustments following stress seem to play

key roles in onset and propagation of mood disorders. To most of us, stress is a beneficial response of our neuronal systems to acute challenges of the exterior world. To put it simply, it is more beneficial for a rabbit to become stressed and flee when it sees a fox approaching. However, severe or repeated stress can lead to detrimental effects on regular neural function.²⁹

Neural plasticity is a term which involves interneuronal communication and adaptation in order to give the appropriate responses to stress or aversive stimuli. One example of such a response could be changes in neurogenesis—the generation of new neurons. Dysfunction of adequate regulatory processing due to severe or chronic stress is capable of disturbing neural plasticity.

Medical treatment with antidepressant agents may bring back regular function of neural systems by influencing neural plasticity: antidepressants require long-term administration, while blockade of the reuptake of serotonin (5-HT) and/or norepinephrine as their most common and initial mode of action is fairly rapid. There is a process whereby neurons can adapt to and regain plasticity while the local biochemical environment is changing due to the application of antidepressants. Thus, the long-term mode of action of antidepressant medication seems much more dynamic and complex than just up- or downregulation of synaptic levels of monoamines.

The role of the hippocampus

The hippocampus is a well-characterized brain structure. In 1886 C. Golgi stained hippocampal neurons with his novel silver impregnation technique, which became known as the Golgi procedure. Since then a great number of neuropsychiatric phenomena have been studied in the hippocampal formation.

The relatively simple organization—pyramidal neurons in the hippocampus proper and the granule cells of the dentate gyrus are arranged in single, densely packed cell layers—is one of the major reasons why the hippocampus has frequently been used as a cytoarchitectural model of the cortex. Recent findings in volumetric neuroimaging studies make a strong case that biochemical changes in the brain carry morphological sequels. So far we have learned that gray matter volumes are diminished in depressed patients and in post-traumatic stress disorder patients in the medial and orbital prefrontal cortex, the mesiotemporal cortex, and the ventral striatum, and are accompanied by an enlargement of the third and the

lateral ventricles.³⁰⁻³³ Hippocampal gray matter volume is reduced strikingly in depressed patients.^{34,35}

Additional postmortem brain studies underpin the above-mentioned results. According to Vincent et al³⁶ there is a layer-specific reduction of interneurons in the anterior cingulate cortex. Significant reduction in numbers of non-pyramidal neurons in the CA2 area of hippocampus was reported in postmortem studies of bipolar disorder.³⁷ Also in regions other than hippocampus, there may be a decline in brain region volume and total cell number.^{38,39}

Elevation of cortisol levels in the elderly correlates with reduced hippocampal volume, and is associated with memory deficits.⁴⁰

Patients with depression have a functional deficit of the hypothalamic-pituitary-adrenal (HPA) axis.⁴¹ Hippocampal neurons are reported to be damaged by exposure to stress or activation of the HPA axis and elevation of glucocorticoids. Taken together, this overview of morphologic evidence strongly supports a functional link between changes at the molecular levels and morphology. The task of future research could be to develop strategies allowing the diseased hippocampus or other affected brain structures to regain regular morphology and function. Focusing on neurogenesis—which is defined as a series of events including proliferation of a neural precursor or stem cell that results in appearance of a new neuron⁴²—may be a systematic as well as pragmatic way to proceed.

There is a growing body of evidence for the phenomenon of neurogenesis in humans.¹⁵ Localization of pluripotent progenitor cells and thus neurogenesis appears to be restricted to certain brain regions, in particular, the sub-ventricular zone (SVZ) and the subgranular layer of the dentate gyrus of the hippocampus.⁴² Neurogenesis in the adult mammalian brain is regulated by genetic and environmental factors⁴³⁻⁴⁵—all leading to the exciting possibility of pharmacological regulation of neurogenesis in the adult brain, and eventually of the disease-related pathophysiological changes.

One of the mainstay therapies in the treatment of recurrent mood disorders, lithium, ranks among such pharmacologic candidates. Lithium increases the levels of the antiapoptotic protein bcl-2.^{46,47} We now know that besides its role in cell cycle control, bcl-2 functions as a neurotrophic factor, since bcl-2 promotes axon regeneration as well as neurite and axonal outgrowth.⁴⁸ In general, neurotrophic factor signaling is mediated both by the phosphatidylinositol-3-kinase pathway and activation of the MAP (mitogen-activated kinase) cascade.^{49,50}

Activation of MAP cascade augments bcl-2 expression. This is very likely to involve the cAMP responsive element binding protein (CREB).⁵¹

CREB is attractive to many researchers because it appears in some way required for long-term memory.⁵² CREB may increase the integrity and functional plasticity of granule cell neurons assuming that CREB is a critical determinant of neural plasticity as well as cell survival. One putative gene target of CREB—and thus of chronic antidepressant treatment—is brain-derived neurotrophic factor (BDNF). There is a functional cAMP responsive element in the exon III promoter of the BDNF gene.⁵³ In the light of this, it is not surprising that local infusion of BDNF in the hippocampus produces an antidepressant effect.⁵⁴

In vitro, activation of the cAMP system upregulates BDNF expression in hippocampal cells.^{55,56} Additionally, BDNF expression effects neuronal depolarization and activation of voltage-dependent calcium channels. These alterations at the synaptic level underlie the influence of BDNF on long-term potentiation.⁵⁷ This underscores the central role of BDNF in neurogenesis considering the pivotal role attributed to BDNF in lineage differentiation of neural stem cells.

Another key player in the pathophysiology and treatment of depression, the biogenic amine 5-HT, should not be neglected, since 5-HT is one of the most extensively studied neurotransmitters of the central nervous system. Moreover, novel findings indicate that 5-HT is particularly relevant to neurogenesis in the hippocampus (*Figure 1*), because in adult rats it has been shown that decreased 5-HT lowers the rate of neurogenesis in the dentate gyrus of hippocampus.⁵⁸ Historically, 5-HT was first described as a serum component augmenting

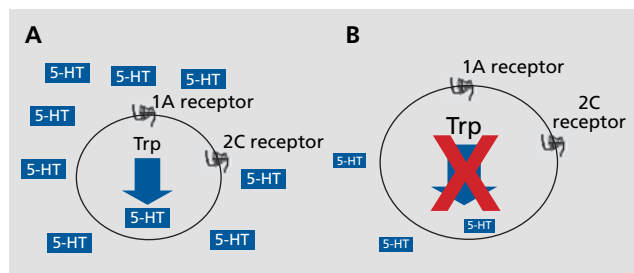


Figure 1. A) Putative model of the serotonergic (5-HT) machinery in adult neural stem cells. Tryptophan hydroxylases (TPH) produces 5-HT, which controls its own metabolism mainly via 5-HT_{1A} and 5-HT_{2C} receptors. B) TPH inactivation leads to less 5-HT production—model proposed by the author based on own experimental data (Benninghoff et al, unpublished data).

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smooth muscle contraction.⁵⁹ In such non-neural systems, 5-HT has been a potent mitogen.^{60,61}

In the brain, 5-HT is among the most widely distributed neurotransmitters. All serotonergic fibers originate in the brain stem raphe nuclei. By way of extensive synaptic connections of the serotonergic fibers, 5-HT contributes to many physiologic functions such as endocrine and circadian rhythms, food intake, sleep, reproductive activity, and motor function, as well as cognition, mood, and anxiety.⁶² In the brain we currently know of 16 different cloned receptor types and subtypes, but it can be expected that their number will grow even further in the near future. In contrast to the multitude of 5-HT receptors, there is only a single 5-HT transporter (5-HTT) responsible for the reuptake of 5-HT into serotonergic neurons after its release into the synaptic cleft. As our own studies have shown, 5-HTT does not have a large impact on neurogenesis.⁶³

A possible role for 5-HT as direct mediator of granule cell generation is currently discussed, since elevated 5-HT levels in the hippocampus increase the rate of proliferation of granule cell precursors.⁶⁴ Epidermal growth factor (EGF) is believed to exert an essential function on the generation and maintenance of neural stem cells. It is therefore not surprising that in non-neural systems, EGF and 5-HT can augment the rate of cell proliferation in a synergistic manner.⁶⁵ BDNF again seems involved in mediating the effects of 5-HT. Thus, chronic administration of 5-HT-selective reuptake inhibitors, clinically used as antidepressants, leads to upregulation of BDNF mRNA.⁶⁶

As already mentioned above, 5-HT exerts its action through a large family of receptors in the periphery and throughout the CNS.⁶² A possible role for the 5-HT_{1A} receptor in the modulation of anxiety and depression, as well as in the mode of action of anxiolytic and antidepressant drugs, has been suspected for many years.⁶⁶ 5-HT_{1A} receptors operate both as somatodendritic autore-

ceptors and postsynaptic receptors. Research regarding 5-HT_{1A} receptor has shown⁶⁷ that the effect of antidepressants upregulating extracellular serotonin levels worked via the 5-HT_{1A} receptor subtype, thus opening a link between our in vitro system, neurogenesis, and clinical relevance in terms of affective disorders.

Although the serotonin hypothesis of depression⁶⁸ is very attractive in this regard, it should not be omitted here that there are additional compelling findings dealing with other neurotransmitting systems, eg, supporting cholinergic mechanisms.⁶⁹ Riederer et al⁷⁰ came to the conclusion that a brain area-specific imbalance of neurotransmitters leads to the clinically different manifestations of depression. The loss of regional interneuronal homeostasis must not necessarily affect huge brain areas; it might be only limited to certain small and circumscribed regions in the brain. As a consequence, clinicians should be able to choose the pharmacologically appropriate medication for the affected brain region.⁷¹

Concluding remarks

Stem-cell maintenance and generation take place in a distinct microenvironment where appropriate external signals can best exert their regulatory function on these cells. Signals provided by neural growth factors are responsible for neural stem-cell growth. Since components of regular stem-cell maintenance like BDNF are also implicated in mechanistic models characteristic of mood disorders, they thus offer new targets for pharmacologic intervention in neuropsychiatric disease. More thorough knowledge about this complex connection may help us render antidepressant treatment more efficient and reduce the undesirable side effects that impair patient compliance. So far there is no stem-cell-based approach really on the horizon for treating depression or any other psychosis. □

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Acercamiento a las células madre en psiquiatría: desafíos y oportunidades

La exploración de las células madre es una tarea fascinante, especialmente en una disciplina donde el empleo de ellas parece exagerado a primera vista, como es el caso de la psiquiatría. En este artículo se quiere entregar una breve panorámica de la situación actual en relación con el tratamiento de las enfermedades mentales. Por razones que serán explicadas, esta revisión se centrará en los trastornos afectivos. La sección siguiente dará cuenta más detallada de la biología de las células madre, incluyendo las propuestas actuales de la ciencia básica que se presentan en técnicas tanto *in-vivo* como *in-vitro*. La parte final se orientará hacia las perspectivas futuras del empleo de estas células madre para la cura de las enfermedades mentales, y se discutirán los desafíos y oportunidades relacionadas con ellas.

Approches des cellules souches en psychiatrie : défis et perspectives

Explorer les cellules souches est passionnant, surtout dans un domaine comme la psychiatrie où, au premier abord, leur utilisation semble incongrue. Cet article souhaite offrir un aperçu de la situation actuelle en rapport avec le traitement des maladies mentales et, pour des raisons qui seront données ultérieurement, il ne traitera que des troubles de l'humeur. La première partie détaillera la biologie des cellules souches, y compris les approches scientifiques actuelles des techniques *in vivo* et *in vitro*. Ensuite, les perspectives d'utilisation des cellules souches dans le traitement des maladies mentales seront présentées et les défis et opportunités qui y sont liés seront discutés.

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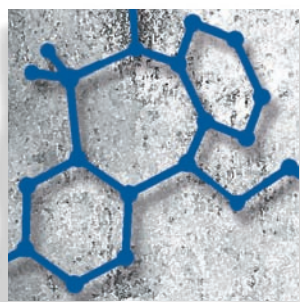
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Pharmacological aspects

Pharmacogenetics of antipsychotic-induced side effects

Todd Lencz, PhD; Anil K. Malhotra, MD



Currently available antipsychotic drugs (APDs) carry significant, though highly variable, liability to neurologic and metabolic side effects. Pharmacogenetics approaches offer the possibility of identifying patient-specific biomarkers for predicting risk of these side effects. To date, a few single nucleotide polymorphisms (SNPs) in a handful of genes have received convergent support across multiple studies. The primary focus has been on SNPs in dopamine and serotonin receptor genes: persuasive meta-analytic evidence exists for an effect of the dopamine D2 and D3 receptor genes (DRD2 and DRD3) in risk for tardive dyskinesia (TD) and for an effect of variation at the 5-HT2C receptor gene (HTR2C) for liability to APD-induced weight gain. However, effect sizes appear to be modest, and pharmacoeconomic considerations have not been sufficiently studied, thereby limiting clinical applicability at this time. Effects of these genes and others on risk for TD, extrapyramidal side effects, hyperprolactinemia, and weight gain are reviewed in this article.

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Dialogues Clin Neurosci. 2009;11:405-415.

Keywords: antipsychotic drug; pharmacogenetics; side effect; tardive dyskinesia; weight gain; dopamine; serotonin

Background

Schizophrenia (SCZ) is a disease with an estimated lifetime morbid risk approaching 1% worldwide,¹ and its public health consequences (mortality and morbidity) are severe. SCZ is associated with an increase of at least 50% in mortality rates compared with the general population,² including a suicide rate of approximately 5%,³ resulting in 10-year average lifespan reduction.⁴ SCZ accounts for nearly 3% of all years lived with disability⁵; amongst individuals aged 15 to 44, SCZ is the third-leading cause of disability.⁶

Despite the demonstrated efficacy of antipsychotic drugs (APDs) in short-term placebo-controlled clinical trials, long-term outcomes frequently remain unsatisfactory. The largest NIH-supported clinical trial of antipsychotic agents conducted to date revealed that both first-generation antipsychotics (FGAs) and second-generation antipsychotic (SGA) agents have limited long-term effectiveness, largely due to high rates of discontinuation (~75% discontinuation within 18 months).⁷ Similar results were obtained in two large-scale European effectiveness trials.^{8,9} In each of these trials, clinically significant side effects were noted in the majority of patients, and tolerability was the primary cause of at least 20% of all drug discontinuations.

Author affiliations: Center for Translational Psychiatry, Feinstein Institute for Medical Research, North Shore – Long Island Jewish Health System, Glen Oaks, NY, USA; Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore – Long Island Jewish Health System, Glen Oaks, NY, USA; Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine, Bronx, NY, USA

Address for correspondence: Anil K. Malhotra, Division of Psychiatry Research, The Zucker Hillside Hospital, 75-59 263rd Street, Glen Oaks, NY 11004, USA (e-mail: malhotra@lij.edu)

Pharmacological aspects

Selected abbreviations and acronyms

5-HT	<i>serotonin</i>
APD	<i>antipsychotic drug</i>
EPS	<i>extrapyramidal symptom</i>
FGA	<i>first-generation antipsychotic</i>
SCZ	<i>schizophrenia</i>
SGA	<i>second-generation antipsychotic</i>
SNP	<i>single-nucleotide polymorphism</i>
TD	<i>tardive dyskinesia</i>

The high likelihood of medication discontinuation has substantial clinical and economic implications, as treatment nonadherence is perhaps the single strongest predictor of relapse and rehospitalization.¹⁰ Patients who have discontinued APDs may be as much as five times more likely to relapse as medicated patients.¹¹ Moreover, nearly half of rehospitalization costs in SCZ may be accounted for by medication nonadherence.¹² In addition to the effectiveness trials cited above, many observational studies and controlled trials have presented evidence that perceived side-effect burden frequently leads to both poor attitudes towards medications and a tendency towards discontinuation, nonadherence, and partial adherence.^{13,14} Although side effects are highly prevalent, there is also substantial variability in liability to clinically significant or intolerable adverse events.¹⁵ Consequently, understanding and predicting liability to side effects may be an effective strategy to improve prognosis in schizophrenia.

Antipsychotic-induced side effects

FGAs were most commonly associated with neuromuscular side effects, including the potentially irreversible movement disorder, tardive dyskinesia (TD).¹⁶ In large cohort studies, TD has been shown to affect at least one in five, and perhaps as many as one in three, patients treated chronically with FGAs.¹⁷ New onset (incidence) of TD is approximately 3% to 5% per year of treatment, and these rates are increased as much as fivefold in elderly patients.¹⁸ In addition to physical discomfort and social stigma, presence of TD has been associated with reduced quality of life, increased psychopathology, and increased mortality rates.¹⁹ Even at low doses and/or intermittent treatment schedules, the high prevalence and morbidity associated with TD was the primary impetus for the promotion of SGAs as preferred first-line treatment, at least in the United States.^{15,20} Although

use of SGAs is not entirely free from TD risk, incidence and rates are as much as 80% lower for SGAs compared with FGAs.^{21,22}

Though treatable and reversible, extrapyramidal symptoms (EPS) including Parkinsonian motor difficulties as well as akathisia, are highly prevalent with FGAs and are also associated with patient discomfort, dissatisfaction, and discontinuation of treatment.¹⁶ Despite the initial optimism that SGAs would greatly reduce EPS burden, most SGAs still demonstrate a clinically relevant tendency to induce these symptoms.^{23,24} In a large-scale effectiveness trial in chronic SCZ patients, SGAs were indistinguishable from a low-dose FGA (perphenazine) in rates of new onset of akathisia and EPS (5% to 10% each, irrespective of drug assignment).²⁵ However, meta-analytic reviews of the literature demonstrate that overall EPS burden may be reduced by 30% to 50% with SGAs.²⁶ Because the mechanism of action for all currently approved antipsychotic medications remains blockade of dopamine receptors,²⁷ motor and other side effects (eg, prolactin elevation) remain a concern in the treatment of SCZ.

While SGAs have moderately reduced EPS and substantially reduced TD liability relative to FGAs, these newer antipsychotics are most notable for their propensity to induce weight gain,²⁸ as well as related metabolic disturbances such as hypertriglyceridemia and hyperglycemia.²⁹ Clozapine and olanzapine are the APDs most frequently associated with weight gain, but all APDs, even first-generation agents, seem to share these effects as a group to varying degrees.³⁰ For example, a large-scale effectiveness trial in antipsychotic naïve patients demonstrated clinically significant weight gain ($\geq 7\%$ of baseline) in more than half of patients treated with haloperidol.⁹ Obesity has serious implications for overall health and survival due to an increased risk for cardiovascular and malignant disorders³¹; these risks may be of particular importance in patients with SZ who often have limited access to health care and decreased motivation for weight reduction secondary to negative symptomatology.¹³ Unfortunately, APD-induced weight gain is very difficult to reverse, even with sophisticated behavioral, dietary, and pharmacological interventions.³²

Pharmacogenetic studies of antipsychotic-induced side effects

While the side effect profile of APDs is extremely burdensome *in the aggregate*, there is substantial interindi-

vidual variation in the degree of any particular motor or metabolic effect for a given patient.¹⁵ Despite extensive research over the last two decades, data on clinical or biological predictors of antipsychotic side effects are limited. A few generalizations can be made, but these are not sufficient for individual-level prognosis: i) both the very old and the very young appear to be more susceptible to most APD-induced adverse events^{18,32}; ii) patients experiencing extrapyramidal symptoms are twice as likely to develop TD as patients who do not exhibit EPS³³; iii) olanzapine and clozapine have greater liability for metabolic effects and reduced incidence of motoric side effects compared with most other agents^{7,9,26,30}; iv) APD dose may be correlated with some of these effects, but the relationship is weak and even low doses may carry substantial risk.^{16,17,32} A priori identification of the patients who will be at a higher risk for development of adverse side effects could help clinicians avoid lengthy ineffective APD trials and limit patients' exposure to drug side effects.

Since the mid-1990s, the field of pharmacogenetics has offered the potential for providing readily accessible, immutable biomarkers—DNA sequence variants—that might be predictive of an individual's propensity for both positive and adverse effects of drugs. However, to date, the promise of personalized medicine has remained unfulfilled. Because academic pharmacogenetic research is often limited to small and clinically heterogeneous samples, individual studies have been unable to provide compelling results. Additionally, the modest effect sizes which are common in complex genetics present an obstacle in the quest for valid biomarkers, which require high sensitivity and specificity for individual clinical prediction. Moreover, examination of disparate polymorphisms across a wide variety of candidate genes has created an impression of scattered, unreplicated findings. Recently, however, a series of findings across multiple laboratories have begun to converge for a few genes related to serotonin and dopamine, the most prominent neurotransmitters targeted by APDs. In the subsequent sections, we will focus on the converging evidence implicating the most well-studied candidates for pharmacogenetic predictors of antipsychotic-induced side effects. Particular emphasis will be placed on single nucleotide polymorphisms (SNPs) that have a sufficient evidence base to have permitted published meta-analytic studies.

Tardive dyskinesia

Tardive dyskinesia is the most extensively studied APD-induced side effect in the pharmacogenetics literature to date. These studies have typically been cross-sectional in nature, with ascertainment based on retrospective identification of cases with varying treatment histories and duration. The ability to study prevalence, rather than incidence in the context of a clinical trial, has permitted cumulative sample sizes in the thousands. It is important to note, however, that this ascertainment strategy may suffer from false negatives (patients with mild or reversible TD) and false positives (patients with acute motoric abnormalities that do not persist). Within this literature, variants within the genes encoding dopamine D2 and D3 receptors have been the primary focus, as detailed below.

Dopamine D2 receptor blockade is a property of all known antipsychotics, as demonstrated in vitro and in vivo,³⁴ yet a predictive relationship between variation in the *DRD2* gene (located on chromosome 11q22) and APD-induced side effects has only been examined in a handful of studies. Most pharmacogenetic studies to date have examined the 3' Taq1A polymorphism (rs1800497), which more recently has been determined to be a nonsynonymous coding SNP in a neighboring ankyrin repeat gene (*ANKK1* Glu713Lys).³⁵ Possibly due to linkage disequilibrium with another site (or sites) within *DRD2* (Figure 1), the minor (T) allele (also called the A1 allele) at rs1800497 has been associated with a 40% reduction in striatal D2 receptor density based on both in vitro assays³⁶ and in vivo imaging studies.³⁷ This allele appears to be protective against TD. As shown in Table 1, two recent meta-analyses (based on overlapping sets of studies) have persuasively demonstrated increased rates of TD in A2 (C) allele carriers.^{38,39} The odds ratio (OR) of 1.30 indicates a 30% increase in risk for TD *per allele*, so that A2/A2 homozygotes are nearly 80% more likely to develop TD as A1/A1 homozygotes. Alternately, it can be said that A1/A1 homozygotes have nearly half the rate of TD compared with A2/A2 homozygotes. However, it is important to note that the A2 allele is the common allele at this SNP, and A1/A1 homozygotes represent <10% of the Caucasian population (A1 allele frequencies are much higher in non-white populations).

Like the D2 receptor, the dopamine D3 receptor is also selectively expressed in the basal ganglia and is consid-

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ered to be a target of antipsychotic action⁴⁵; consequently, several pharmacogenetic studies in schizophrenia have examined the *DRD3* gene, located on chromosome 3q13.3. To date, only one functional SNP (rs6280), a missense variant resulting in a Ser to Gly substitution at amino acid position 9, has been validated for *DRD3*.⁴⁶ The Gly variant has about a 35% allele frequency in non-African populations, and is actually the ancestral allele. The Gly variant has been associated with 4-fold greater dopamine binding affinity in vitro,⁴⁷ resulting in

increased dopamine-mediated cAMP response and prolonged mitogen-associated protein kinase (MAPK) signal.⁴⁸ Several studies⁴⁹⁻⁵² (but not all)^{53,54} have indicated that subjects carrying the Gly variant exhibit enhanced symptom response to treatment with clozapine or risperidone. Concordant with the finding of heightened dopaminergic sensitivity for the Gly allele, multiple studies have demonstrated a significant increase in risk for tardive dyskinesia (TD) amongst Gly carriers. Despite several

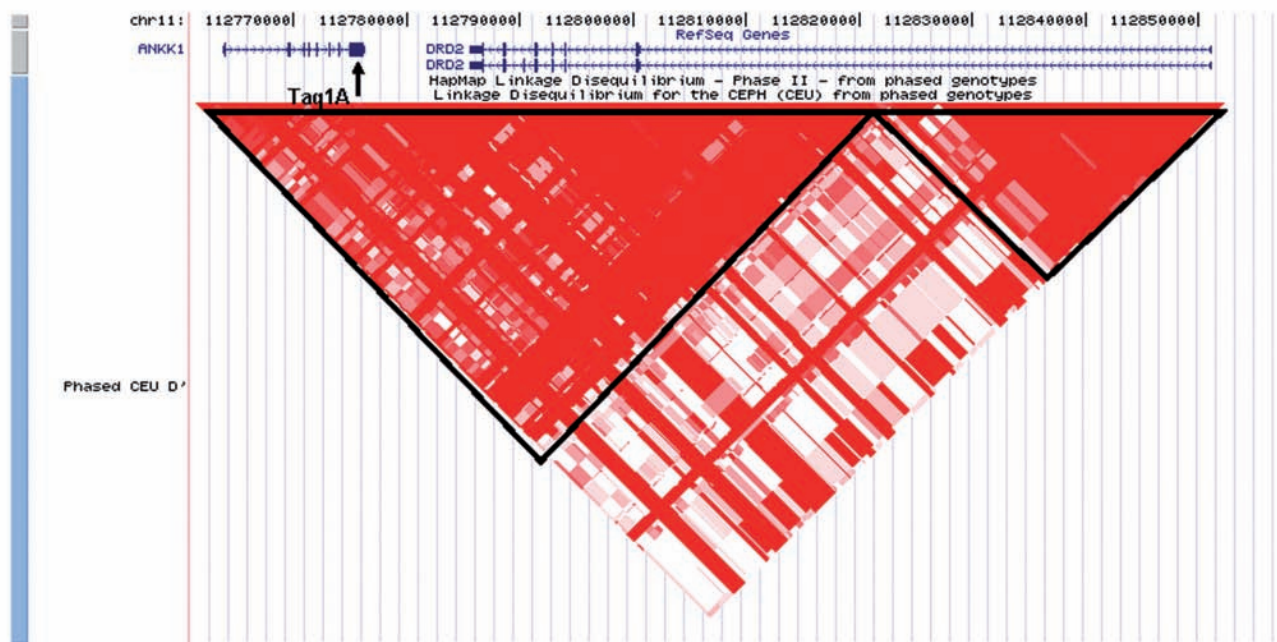


Figure 1. Location of the Taq1A polymorphism in the context of *ANKK1* and *DRD2* at chromosome 11q22. Red triangles represent areas of high linkage equilibrium (D').

Gene	SNP	Allele	No of studies	N patients (with /without TD)	OR	Reference
<i>DRD2</i>	Taq1A (rs1800497)	A2 (C)	6	1256 (507/749)	1.30	Zai et al 2007 ³⁸
<i>DRD2</i>	Taq1A (rs1800497)	A2 (C)	4	764 (297/467)	1.30	Bakker et al 2008 ³⁹
<i>DRD3</i>	Ser9Gly (rs6280)	Gly(C)	8	780 (317/463)	1.33	Lerer et al 2002 ⁴⁰
<i>DRD3</i>	Ser9Gly (rs6280)	Gly(C)	11	1610 (695/915)	1.17	Bakker et al 2006 ⁴¹
<i>DRD3</i>	Ser9Gly (rs6280)	Gly(C)	13	2026(928/1098)	1.16	Tsai et al 2009 ⁴²
<i>COMT</i>	Val158Met (rs4680)	Val(G)	5	1089 (382/707)	1.19	Bakker et al 2008 ³⁹
<i>HTR2A</i>	T102C (rs63113)	C	6	635 (256/379)	1.64	Lerer et al 2005 ⁴³
<i>CYP2D6</i>	Loss of function alleles		8	569 (220/349)	1.43	Patsopoulos 2005 ⁴⁴
<i>SOD2</i>	Ala9Val (rs4880)	Ala(T)	4	680 (134/546)	2.04	Bakker et al 2008 ³⁹

Table I. List of meta-analytic studies of single nucleotide polymorphisms (SNPs) from candidate genes for tardive dyskinesia (TD), with the associated allele and odds ratio (OR) of the association.

negative studies in the literature, three recent meta-analytic studies⁴⁰⁻⁴² indicate that this effect is detectable across a large pooled sample including patients of multiple ethnicities (*Table I*). Intriguingly, a recent study indicates a strong association of the Gly allele with familial essential tremor, the most common inherited movement disorder.⁴⁸ However, the effect size for TD risk is modest (OR=1.16 in the largest meta-analysis), with diminishing effects in the more recent studies of this SNP. This pattern of diminishing effect size estimates over time, termed “the winner’s curse,” is common in genetics studies and can ultimately result in rejection of the initial finding as a false positive.⁵⁵ It is notable that this phenomenon was observed in the context of 13 published studies of *DRD3* Ser9Gly. Moreover, a very recent study in the large CATIE cohort (n=207 cases with TD vs 503 cases without TD), which was not included in any meta-analysis, demonstrated essentially no effects of either *DRD3* Ser9Gly or *DRD2* Taq1A.⁵⁶ Therefore, caution is warranted in the interpretation of other relationships reported across much smaller study sets.

A third dopamine-related gene that has been investigated in multiple pharmacogenetic studies of TD is Catechol O-methyltransferase (*COMT*). While subcortical dopamine activity is primarily terminated by reuptake mediated by the dopamine transporter, a secondary mechanism for dopamine clearance is metabolic degradation via *COMT*.⁵⁷ Additionally, *COMT* is the predominant mechanism of dopamine clearance in frontal cortex. The *COMT* gene contains a functional polymorphism that codes for a substitution of methionine (met) for valine (val) at codon 158. The met allele, which has 36% to 48% allele frequency across various ethnicities, results in a thermolabile protein that has one fourth the enzymatic activity of the val carrying protein.⁵⁸ (In other words, the val allele results in reduced synaptic dopamine due to more rapid clearance). Across five studies meta-analyzed by Bakker and colleagues,³⁹ the val allele was associated with modestly increased risk for TD (OR=1.19; *Table I*). It is unknown whether the protective effect of the met allele is a direct result of subcortical *COMT* activity, or is secondary to alterations (eg, upregulation) in frontostriatal circuitry. In addition to dopamine antagonism, one of the common features of many antipsychotics is near-saturation binding of serotonin (5-HT)₂ receptors, which has been confirmed in vivo using PET imaging.^{59,60} While 5-HT binding is often considered a hallmark of SGAs, it is important to note that serotonergic binding properties are observed for

several FGAs as well.^{61,62} The 5-HT_{2A} receptor gene (*HTR2A*) has been examined in several pharmacogenetic studies of TD; in particular, a promoter region SNP (rs6313), which has been previously associated with response to antipsychotics (as well as antidepressants), has been extensively studied in relation to TD. While these studies generally converge to indicate a modestly reduced effect of the C allele on symptom response,⁶³ this same allele has been associated with significantly *increased* risk for tardive dyskinesia.⁴³ As shown in *Table I*, a recent meta-analysis reported an odds ratio of about 1.6 for C allele carriers across 6 studies; effects were strongest in older patients (age >47 years), and were specifically associated with limb-truncal (but not orofacial) TD.⁴³ Notably, this SNP is a perfect proxy for another promoter region SNP, rs6311 (also referred to as -1438G/A), which appears to affect transcription of the receptor.⁶⁴ Specifically, the G allele (a perfect proxy for the C allele at rs6313) tends to be associated with reduced expression of the receptor. It can therefore be inferred that reduced availability of the 5-HT_{2A} receptor is a risk factor for tardive dyskinesia. Notably, 5-HT_{2A} receptors are strongly expressed in the caudate and putamen,⁶⁵ and recent evidence obtained from dopamine-depleted rodents suggests a complex interplay of subcortical dopamine and 5-HT in the regulation of motor behavior.⁶⁶

Two genes outside of the dopamine and 5-HT systems have received sufficient attention in the pharmacogenetics of TD to merit meta-analysis (*Table I*). Many commonly prescribed APDs, including FGAs (haloperidol, perphenazine, thioridazine), as well as SGAs (risperidone and aripiprazole), are metabolized in the liver by CYP2D6 (debrisoquine hydroxylase).⁶⁷ The CYP2D6 gene is highly polymorphic, with over 70 known variants (for a current classification, view the allele nomenclature at <http://www.imm.ki.se/CYPalleles/>). Homozygosity for null alleles gives rise to the “poor metabolizer” phenotype characterized by no enzyme activity while null allele heterozygosity gives rise to an intermediate debrisoquine hydroxylase metabolic phenotype characterized by impaired—but not absent—enzyme activity.⁶⁸ Reduced CYP2D6 activity can be expected to result in higher effect dose as measured by blood levels of active drug, with potential for increased dose-dependent side effects. Consistent with this pharmacokinetic prediction, a meta-analysis of 8 studies demonstrated a moderate effect of (any) loss of function alleles on risk for TD (OR=1.43), while homozygotes (poor metabolizers) had 1.64-fold

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greater odds of suffering tardive dyskinesia.⁴⁴ A recent small study further confirms these results.⁶⁹ A similar effect has been studied for *SOD2*, the gene encoding manganese superoxide dismutase, a mitochondrial enzyme involved in oxidative metabolism. A functional SNP (Ala9Val), affecting efficiency of MnSOD transport, has been associated with TD risk; counterintuitively, the less efficient val allele is protective.³⁹ Homozygotes for the Ala (T) allele are about twice as likely to develop TD compared with val carriers (*Table I*).

Extrapyramidal symptoms

Compared with the relative plethora of studies on tardive dyskinesia, pharmacogenetic studies of EPS are lacking. However, a few studies have reported allelic effects on acute side effects that are consistent with those reported for TD. For example, Eichhammer et al⁷⁰ reported increased incidence of akathisia amongst *DRD3* Gly carriers; however, two studies of extrapyramidal symptoms have been negative.^{71,72} One additional study identified another *DRD3* SNP (rs167771) which was associated with EPS in a study of 270 risperidone-treated patients,⁷³ but this result awaits replication. One small study has demonstrated an effect on EPS risk for the C allele of rs6313 in *HTR2A* that parallels its effect on TD.⁷¹ Although not previously examined in TD studies, a SNP in *RGS2* (rs4606) has been associated with extrapyramidal symptoms in two studies.^{74,75} Although a third study was negative, this regulator of intracellular dopamine signaling merits additional research.⁷⁶

Prolactin elevation

While prolactin elevation has also not been widely studied across most of the genes listed in *Table I*, there have been seven published studies examining *DRD2* Taq1A.⁷⁷⁻⁸³ As

displayed in *Table II*, these studies have yielded mixed results across a variety of APDs. Notably, the three positive studies all reported that the A1 allele was associated with increased risk for hyperprolactinemia, and a fourth study demonstrated the same effect in females only. This is the opposite allele that was associated with TD, which may reflect the fact that prolactin response is mediated via the tuberoinfundibular pathway (hypothalamus and pituitary).⁸⁴

Weight gain

It has been suggested that increased 5-HT binding profiles may account for the increased liability to weight gain observed in the second-generation antipsychotics.⁸⁵ A survey of the literature of the regulation of feeding behavior points to a major role for 5-HT, with both animal and human investigations showing, in general, that increasing 5-HT results in decreased feeding, with the reverse also true.⁸⁶ Pharmacologic agonists of 5-HT_{2C} lead to decreased feeding in animals⁸⁷ it is logical to speculate that 5-HT_{2C} antagonists, including most second-generation antipsychotics, might lead to increased food intake.

Perhaps the best evidence for a specific role of serotonin-related genetic factors in antipsychotic-induced weight gain is provided by studies of the promoter region polymorphism, -759 T/C (rs3813929), in the *HTR2C* gene (on the X chromosome). Reynolds and colleagues⁸⁸ studied 123 adult drug-naïve Han Chinese SCZ patients treated primarily with risperidone or chlorpromazine. Subjects with the T allele at this locus gained significantly less weight than subjects with the C allele in short-term (6- and 10-week) treatment; none of the 27 subjects with the T allele met criteria for severe (>7%) weight gain after 6 weeks, as compared with 28% of the 96 subjects without the T allele. Two

Reference	Drug	N patients	Allele	Significant?
Calarge et al 2009 ⁷⁷	Risperidone	107	A1 (T)	Yes
Kwon et al 2008 ⁷⁸	Aripiprazole	90		No
Yasui-Furukori et al 2008 ⁷⁹	Risperidone	174		No
Aklillu et al 2007 ⁸⁰	Perphenazine	22	A1 (T)	Yes
Anderson et al 2007 ⁸¹	Risperidone	101		No
Young et al 2004 ⁸²	Various	144	A1 (T)	Yes
Mihara et al 2000 ⁸³	Nemonapride	25	A1 (T)	Females only

Table II. List of studies of the Taq1A polymorphism (rs1800497) from the *ANKK1/DRD2* locus in association with antipsychotic drug-related prolactin levels.

studies^{89,90} also reported an association of the T allele to reduced weight gain in a small samples of clozapine-treated patients, although this effect was only significant in males in one of these. Ellingrod and colleagues⁹¹ reported that the T allele is associated with less weight gain in Caucasian patients treated with olanzapine, and Templeman et al⁹² reported the same for weight gain associated with a mixed group of antipsychotics in a small Spanish first-episode cohort. Recently, Lane et al⁹³ extended these findings to include risperidone (in 123 Han Chinese inpatients), and Ryu et al⁹⁴ demonstrated the same effect for the T allele in 84 Korean inpatients treated on various antipsychotic monotherapies. A few studies, however, have not detected significant associations between -759 T/C and clozapine-induced weight gain⁹⁵⁻⁹⁷ which may reflect the winner's curse, but it should be noted that these studies were restricted to chronic patients with extensive prior treatment. A meta-analysis of 8 studies demonstrated a greater than 2-fold increase in risk for clinically significant (7% to 10% or greater) weight gain from baseline associated with the C allele at this SNP.⁹⁸

Analogous to the aforementioned role of *RGS2* in EPS, one gene involved in intracellular signaling has been repeatedly with respect to APD-induced weight gain. *GNB3* encodes a subunit of a heterotrimeric guanine nucleotide-binding protein (G protein), which integrates signals between receptors and effector proteins.⁹⁹ An SNP polymorphism (C825T) in this gene has been associated with essential hypertension and obesity; this SNP is also associated with relative prevalence of a high-activity splice variant of *GNB3*.¹⁰⁰ According to a recent meta-analysis, five studies have examined effects of this SNP on APD-induced weight gain; the T allele was marginally associated with increased weight gain.¹⁰¹ However, this effect was consistent with its effect on BMI and other metabolic variables in the general population, so the mechanism in the context of APD treatment remains unclear.

Conclusions and future directions

As summarized in the preceding sections, pharmacogenetic studies have begun to converge on a few genetic variants that are replicably associated with the common APD-induced motor and metabolic side effects. However, three factors limit the ability of the field to deliver on the promise of personalized medicine at this time, and point to critical issues for the next generation

of pharmacogenetic studies. First, a treating psychiatrist would be unable to use this information to offer a validated alternative, due to the lack of pharmacogenetic head-to-head comparisons of treatment with differing mechanisms. Second, even fairly consistent single-gene results, such as those observed for *DRD3* and TD, fail to provide large enough effect sizes to make confident clinical decisions. In order to provide a clinically useful test, with sufficient sensitivity and specificity to make confident individual predictions, a combination of SNPs across different loci will be required. Third, the economics of conducting pharmacogenetic tests on a large clinical scale will need to be justified to payers, including the insurance companies and the federal government. In order to do so, pharmacogenetics researchers will need to quantify the beneficial economic impact of tailored prescription practices.¹⁰²

Of course, any personalized clinical decision-making process will optimally include validated predictors of symptom response as well as adverse effects. The variability in symptom response ranges from patients who experience rapid symptom remission to a subset of patients often described as "treatment-refractory."¹⁵ Even when fully adherent with medication, as many as 40% of patients fail to demonstrate adequate response on the hallmark positive symptoms of hallucinations and delusions.¹⁰³ Unfortunately, the literature on pharmacogenetics of response is more difficult to summarize than for side effects; due to wide differences in trial methodology and definition of dependent measures, no meta-analytic studies have been published in the last decade. (One early meta-analysis of clozapine response identified an effect of *HTR2C* T102C, as described earlier.⁶¹) Finally, it should be noted that candidate gene approaches to pharmacogenetics run a dual risk of either an overly restrictive search space, or a potentially overwhelming number of candidates. While initial pharmacogenetic studies have primarily focused on dopamine and serotonin genes, the slow pace of individual candidate gene investigations has resulted in many additional scattered and isolated studies across investigators. On the other hand, the advent of genome-wide association studies (GWAS) provides a hypothesis-free method of generating candidate genes for novel complex phenotypes. Unfortunately, this method carries its own statistical concerns, most notably limitations in statistical power (due to correction for multiple comparisons) in necessarily limited clinical trial samples.

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One way to enhance sample size and statistical power in the short run is to utilize a strategy that permits cross-sectionally defined phenotypes. In a proof of principle study, we have recently utilized the Affymetrix 500K microarray in a sample of our retrospectively-characterized patients with schizophrenia. (Initial case-control analyses were SCZ diagnosis were published for data obtained from the first 322 Caucasian subjects.¹⁰⁴ All subjects self-identified as Caucasian non-Hispanic; testing of 210 ancestry informative markers (AIMs) revealed no evidence of population stratification). In this same sample, we have performed a preliminary analysis examining treatment responsiveness, using clozapine assignment as a proxy for poor response. Detailed chart reviews permitted classification of 97% of the sample. Approximately 35% of patients were assigned clozapine due to treatment nonresponsiveness, and groups were matched on key demographic variables including age, duration of illness, sex, and family history. Despite the small sample for this interim analysis, one SNP nearly obtained genome-wide significance ($P=4.3 \times 10^{-7}$). This SNP neighbors *CNTN4* (contactin-4), a neuronal membrane protein that functions as a cell adhesion molecule, and is thought to be critical for the formation of axon connections in the developing nervous system¹⁰⁵; *CNTN4* has also recently been implicated in autism.¹⁰⁶

In the longer term, much larger prospective studies will be required to achieve to: i) obtain clear estimates for risk parameters; and ii) determine whether application of a pharmacogenetic risk profile is clinically and economically advantageous. Optimally, such studies may focus on the first episode of SCZ, which typically occurs in late adolescence or early adulthood¹⁰⁷ and may be the most critical period in the life of an individual with SCZ. Successful treatment of the initial psychotic episode is crucial for minimizing the cascading effects of social and vocational deterioration.^{108,109} From a methodological perspective, studies of first-episode patients minimize potential confounds associated with chronic illness and variable history of prior treatment; first-episode cohorts are also marked by reduced duration of psychotic symptoms, substance abuse, and functional/social disabilities.¹¹⁰ By contrast, studies of chronic SCZ may systematically over-represent patients who are not fully responsive to treatment or are nonadherent to treatment (or both), and underestimate APD response. First-episode samples may be less biased on these factors and therefore may be more informative about the spectrum of outcomes with APD treatments. While large-scale prospective trials involving first-episode cohorts are logistically challenging, such studies would hold substantial promise for advancing the field in the next decade. □

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Farmacogenética de los efectos secundarios inducidos por los antipsicóticos

Actualmente los fármacos antipsicóticos (FAP) disponibles conllevan, con una alta y significativa aunque variable probabilidad, efectos secundarios neurológicos y metabólicos. Las aproximaciones farmacogenéticas ofrecen la posibilidad de identificar biomarcadores específicos para el paciente para predecir el riesgo de estos efectos secundarios. A la fecha, múltiples estudios han convergido en dar sustento a unos pocos polimorfismos de nucleótidos simples (SNPs) de un pequeño grupo de genes. El foco primario ha estado en los SNPs de los genes de los receptores de dopamina y serotonina; estudios de meta-análisis han demostrado una evidencia convincente para el efecto de los genes de los receptores de dopamina D2 y D3 (RDD2 y RDD3) en el riesgo de disquinesia tardía (DT) y para un efecto de variación del gen del receptor 5HT2C (R5HT2C) en la probabilidad de aumento de peso inducido por los FAP. Sin embargo, la magnitud del efecto parece ser modesta y las consideraciones farmacoeconómicas no se han estudiado suficientemente, por lo que la aplicación clínica en este momento es limitada. En este artículo se revisan los efectos de estos y otros genes en los riesgos de DT, efectos secundarios extrapiramidales, hiperprolactinemia y aumento de peso.

Pharmacogénétique des effets secondaires induits par les antipsychotiques

Les médicaments antipsychotiques disponibles actuellement sont significativement responsables, bien que de façon très variable, d'effets secondaires métaboliques et neurologiques. La pharmacogénétique permet d'identifier des biomarqueurs spécifiques des patients permettant de prédire le risque de survenue de ces effets indésirables. À ce jour, un petit nombre de polymorphismes de nucléotide simple (single nucleotide polymorphism ou SNP) issus d'une poignée de gènes, a été identifié au cours de plusieurs études. Les SNP des gènes du récepteur à la dopamine et à la sérotonine ont été les premiers à être étudiés : des métaanalyses convaincantes ont montré une implication des gènes DRD2 et DRD3 (récepteur à la dopamine D2 et D3) dans le risque de dyskinésies tardives (DT) et celle d'une variation du gène du récepteur HT2C (5-HTR2C) dans la prise de poids due aux antipsychotiques. L'importance de ces effets semble néanmoins modeste et, les considérations pharmacoeconomiques étant insuffisamment étudiées, les applications cliniques restent aujourd'hui limitées. Cet article analyse les effets de ces gènes ainsi que d'autres sur le risque de DT, d'effets extrapyramidaux, d'hyperprolactinémie et de prise de poids.

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Pharmacological aspects

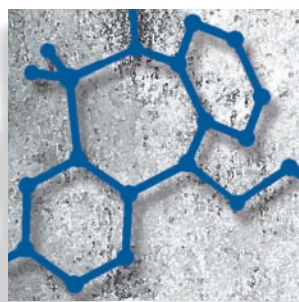
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Pharmacological aspects

Major depression during interferon- α treatment: vulnerability and prevention

Francis E. Lotrich, MD, PhD



Major Depressive Disorder (MDD) during interferon- α (IFN- α) treatment can occur within a few months of therapy, and shares many homologies with other forms of MDD. Most patients are resilient to the side effect of interferon-induced depression (IFN-MDD), but 15% to 40% are vulnerable. Several studies have employed antidepressants to prevent the incidence of an IFN-MDD episode, and the results suggest that prophylactic antidepressants may be specifically useful in those with pre-existing subthreshold depressive symptoms and/or a history of prior MDD episodes. Several other potential markers of vulnerability for IFN-MDD have been implicated in assessments of non-depressed patients before they start IFN- α . These include poor sleep quality, premorbid elevations in inflammatory cytokines, genetic polymorphisms in the serotonin system, personality, and social support. The interplay of these factors strongly predicts who is at risk for IFN-MDD, and indicates several potentially modifiable targets for the personalized prevention of IFN-MDD.

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Dialogues Clin Neurosci. 2009;11:417-425.

Keywords: depression; cytokine; interferon; prevention; resilience; genetics

Author affiliations: Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, USA

Major Depressive Disorder (MDD) is common, costly,^{1,3} and notably heterogeneous. Unfortunately, the accurate prediction and subsequent prevention of MDD episodes (MDEs) has been challenging. There is evidence that MDEs are variously associated with elevated psychosocial stress, the postpartum period, hypothyroidism, circadian changes, cerebrovascular disease, administration of inflammatory cytokines such as interferon- α (IFN- α), etc. Therefore, one approach for preventing a MDE could be to avoid stressful circumstances, pregnancy, cerebrovascular disease, and/or IFN- α therapy. However, this is often impractical. Thankfully, most people who are exposed to these various “triggers” do not develop MDD.

Identifying modifiable markers of risk in specifically vulnerable people, and then mitigating these before MDD occurs, could be a better approach for preventing MDD. However, identifying causal risk factors that pre-exist in nondepressed people requires prospective studies, and the incidence of an MDE over 1 year is less than 2%.⁴⁻⁶ The necessarily large epidemiologic studies have successfully identified predictive risk markers such as gender, age, cohort, family history, marital status, socioeconomic status, and stressful life events^{6,7}—but each of these is difficult or impossible to mitigate. Another strategy is needed for prospectively assessing nondepressed people for modifiable risk factors, and a related strategy is needed for examining whether specifically alleviating these vulnerabilities prevents MDE.

Address for correspondence: Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, USA
(e-mail: lotrichfe@upmc.edu)

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Selected abbreviations and acronyms

IFN-α	<i>interferon-alpha</i>
IL	<i>interleukin</i>
MDD	<i>major depressive disorder</i>
SSRI	<i>selective serotonin reuptake inhibitor</i>

MDD during IFN- α therapy

One approach for delineating modifiable risk factors is to examine homogeneous groups of people who are definitively known to soon be exposed to a specific MDD-evoking situation. Towards this end, patients receiving IFN- α may be ideal candidates for examining MDD vulnerability.⁸⁻¹² MDD during IFN- α treatment (IFN-MDD) typically develops within the first 2 or 3 months of administration,¹³⁻¹⁷ and occurs in about 15% to 40% of patients.¹⁸ Thus, prospectively assessing IFN-MDD onset is feasible—and consequently it may be possible to determine predictive modifiable vulnerabilities in the 15% to 40% who subsequently develop IFN-MDD.

Of course, it is conceivable that IFN-MDD is unique, and that other forms of MDD are completely distinct from it. However, several lines of evidence indicate that IFN-MDD may successfully inform us about MDD in general. First, a variety of studies have found a robust relationship

Signs and symptoms	MDD	IFN-MDD
Anhedonia	Yes	Yes ^{24,29}
Depressed mood	Yes	Yes ^{26,30}
Sleep problems	Yes	Yes ^{26,27,29,32}
Amotivation	Yes	Yes ²⁷
Decreased appetite	Yes	Yes ^{27,28,30}
Concentration changes	Yes	Yes ^{27,29,33-36}
Tearfulness	Yes	Yes ²⁷
Social withdrawal	Yes	Yes ²⁷
Guilt	Yes	Yes ²⁶
Interpersonal sensitivity	Yes	Yes ³⁷
Suicidal ideation	Yes	Yes ^{27,29,38}
Associated symptoms		
Irritability	Yes	Yes ^{26,27,29,30,39}
Increased neuroticism	Yes ^{40,41}	Not known
Care-seeking behaviors	Yes ⁴²	Seen in illness behavior ⁴³
Dependency/acting out regression/somatization	Yes ^{44,45}	Seen in illness behavior ⁴⁶⁻⁵⁰

Table I. Comparison of Major Depressive Disorder (MDD) and interferon- α depressive disorder (IFN-MDD) during interferon- α treatment.

between IFN- α and MDE, including those demonstrating a dose-response relationship,^{19,20} studies with control groups,^{16,19-21} and prospective documentations of worsening depression during IFN- α treatment with a return to baseline mood after discontinuation.²³⁻²⁵ Thus, IFN-MDD is a replicable finding in prospective studies. Second, IFN-MDD has phenomenological resemblance to MDD diagnosed in other situations.²¹⁻²⁴ That is, IFN-MDD is not simply fatigue and malaise but—similarly to MDD—involves anhedonia, depressed mood, irritability, anxiety, social withdrawal, poor concentration, altered sleep, personality changes, and suicidal ideation (*Table I*). Third, MDD and IFN-MDD may share similar pathophysiologic mechanisms, as indicated by various independent lines of investigation:

- Many inflammatory cytokines are elevated during MDD.⁵¹⁻⁵³
- Psychosocial stress can increase the levels of inflammatory cytokines.^{54,55}
- IFN- α and other cytokines can affect central monoaminergic systems plausibly involved in MDD.⁵⁶⁻⁶³
- Peripheral cytokines and IFN- α have access to the CNS through a variety of routes in addition to being synthesized in the brain.⁶⁴⁻⁶⁶
- Endogenous IFN- α mRNA can be induced in the cortex, hippocampus, and hypothalamus, with correlated changes in behavior in animal models of depression.^{64,67}
- Systemic administration of IFN- α and other cytokines can affect amotivation and anhedonia behaviors in rodent models of depression.⁶⁸⁻⁷⁵
- Once IFN-MDD is diagnosed, it responds to treatments that are effective for idiopathic MDD, ranging from selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants to electroconvulsive therapy,^{15,76-85} with about 79% to 85% of patients responding to antidepressants.^{86,87}
- IFN- α administration can influence frontal lobe and anterior cingulate function,^{88,89} dopaminergic activity,⁹⁰ and serotonergic function,⁹⁰⁻⁹³—all of which may contribute to the development of depression in a manner homologous to other types of MDD.

Of further public health significance, the use of IFN- α is not rare. Almost 2% of the U.S. currently has chronic hepatitis C (HCV).⁹⁴ IFN- α is the only FDA-approved treatment for HCV,^{95,96} whereas about 170 million people worldwide have been infected with HCV.⁹⁷ Supporting IFN- α 's widespread use, untreated chronic HCV can lead to cirrhosis, hepatocellular cancer, and liver failure,

resulting in about 10 000 deaths per year in the US,⁹⁸ a rate which exceeds that from acquired immunodeficiency syndrome.⁹⁹ Unfortunately, IFN-MDD can potentially result in suicide,³⁸ dose reduction with risk for viral relapse,¹⁶ discontinuation of treatment,^{100,101} and lower quality of life.^{102,103} Therefore, the two rationales for preventing IFN-MDD are that (i) this is a common and disabling syndrome; and (ii) it may be an ideal strategy for informing us about ways to prevent MDD in general.

Prevention studies of IFN-MDD

A few prophylactic trials using selective serotonin reuptake inhibitors (SSRIs) have transpired. These prevention studies initiated SSRIs in patients who were not currently experiencing any MDE prior to beginning the IFN- α therapy (*Table II*).^{80,83,85,104-107} The first randomized placebo-controlled trial (RCT) was done in patients with metastatic melanoma, using very high doses of intravenous IFN- α . This initial study found strong evidence for prevention of IFN-MDD, with only 2/18 paroxetine-treated patients (11%) developing IFN-MDD, as compared with 45% of the placebo-treated group.⁸⁰ Similarly, in three open-label trials of prophylactic SSRIs given to nondepressed HCV patients, only 3/32 patients (9%) developed IFN-MDD, despite all 32 patients having a prior history of affective disorder. These open-label studies are thus consistent with this RCT study, supporting the conclusion that preventative treatment with SSRIs may be useful.

However, two small RCT studies have now been completed in patients with HCV (*Table II*). Neither study

found IFN-MDD prevention.^{85,106} Prophylactic SSRIs may therefore not be universally effective. Despite these two negative findings, one of these studies did report that 24/29 patients in the placebo group developed elevated depression symptoms compared with 10/23 in the paroxetine group.¹⁰⁶ Additionally, further exploratory analyses indicated that prevention may have been most successful for those subjects who already had high pretreatment baseline levels of depressive symptoms.¹⁰⁶ This would be an example of “indicated prevention” whereby treating “subthreshold” depression symptoms may prevent subsequent worsening to full categorical MDD.¹⁰⁸⁻¹¹¹ It has been well-replicated that higher levels of pretreatment depression symptoms are associated with the development of IFN-MDD,^{18,112-115} and these subthreshold symptoms may be an appropriate target for using preventive SSRIs. Another open possibility is that prophylactic SSRIs specifically prevented IFN-MDD in those with past histories of MDD in remission. This type of prevention would be consistent with the use of antidepressants to prevent recurrence of remitted MDD.¹¹⁶⁻¹¹⁹

To explore this latter possibility, we prospectively followed 31 patients who were not depressed at the onset of IFN- α therapy (as determined using a Structured Clinical Interview of DSM-IV Axis I diagnoses). All of these patients had no MDEs within 6 months prior to starting IFN- α , but they did have a history of past MDD. Ten of these patients were stably taking SSRIs. Only 20% (2/10) of the patients on SSRIs developed IFN-MDD, while 47.6% (10/21) not on antidepressants did. These results are numerically similar to the RCTs reviewed above. This very limited analysis suggests a

SSRI	Trial type	(N)	Baseline characteristics	Diagnosis	Comments
Paroxetine ⁸⁰	RCT	18 vs 20	Melanoma patients; average HAM-D>5	DSM-IV	Prevented IFN-MDD. 2/18 vs 9/20
Paroxetine ⁸⁵	RCT	14 vs 19	Average HAM-D<3	DSM-IV	Did not prevent IFN-MDD. 5/14 vs 6/19
Paroxetine ¹⁰⁶	RCT	23 vs 29	Median MADRS = 3	DSM-IV or MADRS>15	Did not prevent IFN-MDD overall 3/23 vs 6/29 Benefit for patients with baseline MADRS >3
Citalopram ¹⁰⁴	Open label	10 vs 0	MDD history in remission	HAM-D =17	1/10 had recurrence of IFN-MDD
Paroxetine or Citalopram ¹²⁰	Open label	8 vs 0	History of previous IFN-MDD (Comparison with prior IFN- α trial)	HADS>8	0/8 had recurrence of IFN-MDD Small average increase in HADS scores
Citalopram ¹⁰⁷	Open label	14 vs 11	Average MADRS >10; History of affective disorder	DSM-IV	2/14 developed IFN-MDD vs 7/11 in the comparison group
Various	Open label	10 vs 21	History of any DSM-IV affective disorder	DSM-IV	2/10 developed IFN-MDD vs 10/21 in the comparison group

Table II. Studies examining prevention of IFN-MDD using antidepressants. Three randomized placebo-controlled trials (RCT), and four open-label studies examining the prevention of major depressive disorder (MDD), diagnosed using criteria from the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), the Hamilton Depression rating scale (HAM-D), or the Montgomery-Asberg Depression Rating Scale (MADRS).

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more targeted use of SSRIs to prevent recurrence, limiting prophylactic SSRI to those patients who are known to have past MDD histories.

However, all of these studies have been very limited in size, and therefore power. Assessing all of the six published prevention studies and our open-label data combined—in a very exploratory type of meta-analysis—15/97 (15%) patients receiving SSRIs prior to starting IFN- α developed IFN-MDD, compared with 36/99 (36%). This is a significant difference, $\chi^2=8.2$; $P<0.001$. However, limiting the meta-analysis to the three RCTs, 10/55 (18%) subjects randomized to pretreatment paroxetine developed IFN-MDD while 21/68 (31%) randomized to placebo did. The trend is numerically similar to the larger meta-analysis, but does not have the power to be significant in a chi-square test ($\chi^2=1.98$).

At this point, only tentative conclusions are possible: (i) Prophylactic SSRIs may plausibly cut in half the incidence of IFN-MDD. To conclusively determine this, however, will require a larger-size trial than those performed to date; (ii) SSRIs may specifically benefit subjects with either pre-existing depressive symptoms (ie, subthreshold depression) and/or a history of prior MDD. This is consistent either with studies of “indicated prevention” in which patients with subthreshold depression are prevented from worsening to full categorical MDD by about 30%,¹⁰⁸⁻¹¹⁰ or with studies preventing recurrence of MDD.¹¹⁶⁻¹¹⁹ A more targeted prevention RCT would be valuable to examine these two possibilities; (iii) Even if SSRIs are found to be effective prophylactics for some people, about 15% to 20% of patients still developed IFN-MDD even when prescribed SSRIs, therefore antidepressants may not be universally effective. Other targets and approaches for prevention are needed; (iv) Most importantly, about half of the patients with a history of MDD remain resilient even during IFN- α treatment. Identifying the source of this resilience for potential replication in other patients would be beneficial.

Modifiable risk factors for IFN-MDD

The goal for this work is preventative treatments that can be targeted towards specifically mitigating those mechanisms underlying vulnerability. Poor sleep quality prior to IFN- α treatment may be one such risk factor.^{121,122} Patients with scores greater than 10 on the Pittsburgh Sleep Quality Index, a validated self-report assessment of sleep quality,¹²³ were ten times more like

to subsequently develop IFN-MDD than patients sleeping better than this.¹²² This large effect size was evident even when controlling for other depression symptoms. It is also consistent with large epidemiological studies wherein insomnia predicted the subsequent development of MDD over follow-up intervals of 1 to 35 years.¹²⁴⁻¹²⁷ As many treatments for sleep exist, this may be a potentially modifiable risk factor for preventing IFN-MDD. This has previously been suggested for MDD,¹²⁸ but may now be readily testable in patients about to be treated with IFN- α .

There is also evidence that increased age may be another risk factor for IFN-MDD,¹²⁹ although this is certainly not a consistent finding.^{130,131} Despite the fact that age itself is not modifiable, this could indicate the presence of age-related modifiable risk factors. Related to this, elevated levels of inflammatory cytokines, such as interleukin-6 (IL-6), prior to IFN- α therapy have been associated with subsequent IFN-MDD.^{132,133} Additionally, a polymorphism in IL-6 that has been associated with increased IL-6 levels is predictive of IFN-MDD.¹³⁴ In the subset of people with increased IL-6 during IFN- α administration, the IL-6 levels temporally predicted next month's depression symptoms.¹³³ This is consistent with cross-sectional studies in which elevated IL-6 levels are associated with MDD.^{54,132,135-140} Thus, increased IL-6 may be another plausibly modifiable target for preventive intervention in depressed individuals. Interestingly, IL-6 increases with age but can be modified by diet¹⁴¹ and/or exercise.^{142,143}

Potential premorbid risk factors for IFN-MDD that may be modifiable through psychosocial interventions could include social isolation¹⁴⁴ and neuroticism.^{115,145} However, when controlling for other premorbid risk factors, the effect size for these is fairly small.¹⁴⁶ Another risk factor may be a hyperactive stress response in the hypothalamic-pituitary-adrenal (HPA) axis.¹⁴⁷ Given the common association between abnormalities in the HPA axis and MDD,¹⁴⁸⁻¹⁵⁰ this may also be a potentially useful predictive marker. Interestingly, HPA axis responsiveness can be therapeutically modifiable by antidepressants.¹⁵¹⁻¹⁵⁴ It is therefore plausible that patients with overactive HPA responses may be the subjects who benefit most from antidepressant prophylaxis. Consistent with this, stress-reactivity did correlate with depressive symptoms prior to IFN- α therapy¹⁴⁷—and thus elevated stress-reactivity may be a potential predictor of the need for “indicated” SSRI prevention.

Genetic polymorphisms within the serotonergic system have also been associated with vulnerability to IFN-

MDD.^{134,146,155} Two studies have replicated the finding that a short allele in the serotonin transporter robustly increases risk for IFN-MDD.^{134,146} Vulnerability to tryptophan depletion has also been associated with polymorphisms in the 5-HT reuptake transporter.⁵⁹ Because IFN-MDD has been associated with lowered tryptophan levels during treatment,^{57,91,93,156} this suggests that differences in serotonergic tone may leave some people vulnerable to IFN-MDD. It is also plausible that these are the same subjects who may benefit from SSRI prophylaxis, a possibility that requires testing.

Interestingly, gender has not been a consistent predictor of IFN-MDD,^{37,157,158} which suggests that IFN-MDD may be partially distinct from some forms of MDD that are unique to females. Also, as long as patients remain abstinent, a past history of drug and alcohol abuse is not predictive of increased risk.^{15,37,131} This suggests that risks for drug and alcohol abuse are distinct from risk for IFN-MDD. One critical implication is that a past history of drug use, in remission, is not a contraindication to prescribing IFN- α . Nonetheless, several leads are now suggested by these various predictive risk factors, several of which may be amenable to modification. The IFN-MDD paradigm has now been used in several studies to examine whether SSRIs can prevent depression. It may now be useful to determine whether other preventive treatments are effective.

Other populations at selective risk for MDD

In summary, encouraging results indicate that: (i) specific patients may be at elevated risk for IFN-MDD; (ii) this

vulnerability may be identifiable prior to IFN- α treatment; (iii) some sources of this vulnerability (such as poor sleep) may be modifiable; and (iv) therefore personalized prevention is testable and could become a reality. Because of the high incidence of IFN-MDD in the first few months of treatment, and the ability to recruit nondepressed patients prior to IFN- α treatment, examining these possibilities appears to be practical and feasible in this population. Several studies with prophylactic SSRIs have already occurred. Furthermore, because of the homologies between IFN-MDD and MDD in general, any lessons learned from IFN-MDD may be translatable to other types of MDD. As examples, MDD occurs at higher rates in populations with multiple chronic illnesses,¹⁵⁹ during bereavement,¹⁶⁰ in caregivers of demented patients,¹⁶¹ in stroke survivors,¹⁶²⁻¹⁶⁴ in postpartum mothers,^{110,165,166} and there is preliminary evidence that MDD incidence could potentially be reduced in these settings.^{161,167} Similar to IFN-MDD, most people in these settings are resilient to developing MDD, with only a subset who are vulnerable.¹⁶⁸

Conclusion

It remains an intriguing possibility that modifiable risk factors identified for IFN-MDD may also be modifiable risk factors in these other settings. Thus, targeting the appropriate prevention to the appropriate patient may be possible, and this may soon lead to the personalized prevention of MDD. □

This work was supported in part by NIMH grant K23MH074012.

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Depresión mayor durante el tratamiento con α -interferón: vulnerabilidad y prevención

El trastorno depresivo mayor (TDM) durante el tratamiento con α -interferón (α IFN) puede presentarse a los pocos meses de terapia y comparte muchas características con otras formas de TDM. La mayoría de los pacientes son resilientes al efecto lateral de la depresión inducida por interferón (TDM-IFN), pero el 15% a 40% es vulnerable. Varios estudios han utilizado antidepresivos para prevenir la incidencia de un episodio de TDM-IFN y los resultados sugieren que los antidepresivos profilácticos pueden ser empleados específicamente en quienes tienen síntomas subumbrales pre-existentes y/o una historia de episodios previos de TDM. Se han propuesto varios potenciales marcadores de vulnerabilidad para el TDM-IFN en la evaluación de pacientes no depresivos antes de iniciar el α IFN. Estos incluyen una mala calidad del sueño, aumento premórbido de las citoquinas inflamatorias, polimorfismo genético en el sistema serotoninérgico, personalidad y apoyo social. El interjuego de estos factores predice en forma importante quién está en riesgo de un TDM-IFN y señala varios blancos potencialmente modificables para una prevención personalizada del TDM-IFN.

Dépression majeure au cours d'un traitement par interféron- α : vulnérabilité et prévention

Un épisode dépressif majeur (EDM) peut survenir au cours des premiers mois d'un traitement par interféron- α (IFN- α), montrant des similitudes avec les autres formes de dépression caractérisées. La plupart des patients présentent une résilience à cette dépression induite par l'interféron mais 15 à 40 % y sont vulnérables. Plusieurs études ayant utilisé des antidépresseurs pour prévenir la survenue d'un EDM lié à l'IFN (IFN-EDM) ont montré qu'une prophylaxie antidépressive peut être utilisée spécifiquement chez les patients ayant une symptomatologie dépressive infraclinique et/ou des antécédents d' EDM. Des patients non dépressifs ont été testés avec des marqueurs potentiels de susceptibilité aux IFN-EDM avant de débiter un traitement par IFN- α . Ils incluent un sommeil de mauvaise qualité, une augmentation prémorbide des cytokines inflammatoires, des polymorphismes génétiques du système sérotoninergique, des éléments de la personnalité et de l'environnement social. L'interaction de ces facteurs prédit fortement qui est à risque d'IFN-EDM et constitue certaines cibles potentiellement modifiables dans le cadre de la prévention personnalisée de l'IFN-EDM.

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Personalized medicine in psychiatry: ethical challenges and opportunities

Kathinka Evers, PhD



Pharmacogenomic developments hold promise for personalized medicine in psychiatry with adjusted therapeutic doses, predictable responses, reduced adverse drug reactions, early diagnosis, and personal health planning. The prospects are exciting, but at the same time, these new techniques stand faced with important scientific, ethical, legal, and social challenges that need to be met in order for the scientific advances to be responsibly applied. This review discusses the ethical balance between challenge and opportunity of personalized medicine in psychiatry under the aspects of adequacy, cost:benefit ratio, and therapeutic equity. It is argued that the promising nature of these therapeutic possibilities makes it all the more important to avoid exaggerating the expectations, and that a sophisticated social infrastructure needs to be developed in order to ensure the realistic and responsible application of personalized medicine in psychiatry.

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Dialogues Clin Neurosci. 2009;11:427–434.

Keywords: psychopharmacology; pharmacogenomics; personalized medicine; promotion versus hype; cost:benefit ratio; therapeutic equity

Author affiliations: Centre for Research Ethics & Bioethics, Uppsala University, Sweden

Pharmacological developments in the 20th century have produced a wide range of drugs that have greatly improved the treatment of many serious diseases. In psychopharmacology, the discoveries of antipsychotic, tranquillizing, or antidepressant agents, such as selective serotonin reuptake inhibitors (SSRIs), were milestones in the treatment of mental illness. However, compared with the general pharmacological progress, the psychopharmacological development, whilst noteworthy, has been somewhat less spectacular. Despite heavy investments in mental health-related research,¹ there have been few important discoveries since the 1950s, when a number of psychopharmacological agents were discovered that are still in use. For example, clozapine was synthesized over 50 years ago but continues to be described as the “most effective antipsychotic drug” for the treatment of schizophrenia,² and is recommended in the UK National Institute of Health and Clinical Excellence (NICE) 2009 update to its schizophrenia guidance.³

Traditionally, the drugs developed have been “one size fits all,” ie, standardized drugs targeting symptoms or syndromes that can be shared by various diseases, rather than being disease-specific, let alone patient-specific. Even though health care is by definition personalized in the sense that the patient’s needs broadly determine the nature of recommended treatment, eg, type and dosage of medication, traditional medication leaves little room for individual variations in responses to treatment, notably through the randomized double-blind procedure used in clinical trials that is incompatible with individu-

Address for correspondence: Centre for Research Ethics & Bioethics, Uppsala University, Uppsala Science Park, SE-75185 Uppsala, Sweden (e-mail: kathinka.evers@crb.uu.se)

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alized assessment. This can be regarded both as a strength, because the structure of the trials ensures that known or unknown confounding factors are evenly distributed between the treatment groups, thus yielding accurate results; or as a weakness because individuality is not taken into account. For better or for worse, drugs are not individually developed; they do not target the individual biological system.

However, human individuals are, biologically as well as socially, highly varied, and a common medical problem is that people with similar symptoms, or the same illness, may react quite differently to a prescribed drug. Even if available data justify the prescription of a given drug, the effects of this drug can vary extensively between distinct individuals. Whereas one individual may be greatly helped by the drug, another may be more or less non-responsive to it; and whilst one patient will suffer severe side effects, another will not. From the point of view of the patient, it is clearly of interest to know if one belongs to the group (normally, the majority) that is helped by the drug, or to the minority that is not, whether one will suffer side effects, and, if so, of what type and degree. For society, adverse drug responses (ADRs) are a major medical and economic problem. ADRs cause thousands of deaths and serious injuries yearly, and have even been suggested to constitute between the fourth and the sixth leading cause of death in the US, which would rank ADRs ahead of pneumonia and diabetes.⁴ Thus the concern felt by many people regarding what side effects they are likely to experience is very valid: even a brief glance at the most common or important side effects may be rather alarming. The side effects of psychopharmacological drugs can be very serious, including loss of muscular coordination, slowing of reactions, addiction, and psychiatric conditions other than the one targeted by the drug (eg, depression or anxiety).

The prescription of drugs that may have serious side effects is not a satisfactory area for a trial-and-error strategy, by which one might prescribe or take a drug with reasonable hope for good results but without knowing in advance what will happen. Even if side-effect profiles are admittedly dynamic, the risk:benefit ratio positive, serious side effects statistically uncommon, and prescription of the drug in agreement with the gold standard of psychiatric treatment in a given context, a physician or a patient might *still* hesitate to prescribe or take it, and wish to know if her/his individual biological struc-

ture is compatible with the drug or not. Will the drug help? If so, at what price? What can be done to optimize its therapeutic effects?

Until recently, there were no options available other than a probability calculus based on data collected from previous and ongoing experience. There were scant possibilities to determine in advance how the patient as an individual would react to the drug. Unsatisfactory, perhaps, but unavoidable: he or she had to take it to find out, a fact that we have “generally accepted with a certain fatalism.”⁵

The door to making such informed individual predictions was opened when, in the mid 1950s, the link between genetic makeup and drug metabolism was identified⁶; ie, when it was discovered that the causes for individual variation in drug response could be genetic.⁷ More precisely, when the *extent* to which the causes of diverse drug response could be genetic was realized, for the genetic determination of the capacity of an organism to respond to its environment has long been accepted in biology,⁸ including the implication of enzymes in the detoxification of foreign substances.⁹ In addition to non-genetic and environmental causes and lifestyle factors, eg, age, gender, family support, good diet, care in following prescriptions, etc, variations in DNA sequence among individuals (genetic polymorphisms) were also found to be involved in the response to drug therapies.¹⁰ Accordingly, knowledge of the individual genome became strongly relevant to drug prescription.¹¹

Increasing knowledge of the human genome has given rise to the development of genomic medicine, genetic testing, and also helped in diagnosing some unusual disorders; still, the impact of genetics in medicine during the 20th century was relatively modest.¹² The recent development of new technologies for genetic testing has promoted new studies in how drugs and genes interact with potentials for much larger impact.¹³ Pharmacogenetics (a term coined in the 1950s¹⁴) is the study of individual variations in drug response due to heredity. It can be distinguished from pharmacogenomics, a broader term denoting all genes in the genome that may influence drug response, but the terms are often used interchangeably.¹⁵ There is considerable hope that new and more effective treatments for numerous mental disorders can result if drugs are developed that specifically target the responsible genes, eg, schizophrenia susceptibility genes.¹⁶

If drug prescription can be personalized, ie, tailored to suit the individual's genetic makeup,¹⁷ this holds promise

of enormous benefits in terms of, notably, personalized medication with adjusted therapeutic doses, predictable drug responses, reduced ADRs, and personal health planning.¹⁸ It should be noted that personalization and individualization, depending on how the concepts are interpreted, need not mean the same thing, and that they are in this context a matter of degree. Here, “personalized medication” can logically, but not realistically, be interpreted as medication developed to suit the singular individual. The realistic interpretation is that personalized medication is “relatively individualized” in the sense of drugs having a more limited group specificity than the earlier “one size fits all” drugs.

Other suggested benefits are considerable time and cost reductions in the pharmaceutical development,¹⁹ and the possibility of pharmacogenomics to simplify the clinical trial process.²⁰ The prospects are exciting, but at the same time, these new techniques stand faced with important ethical, legal, and social challenges that need to be met in order for the scientific advances to be responsibly applied. Below, the ethical balance between challenges and opportunities of personalized medicine in psychiatry from the points of view of adequacy, cost, and therapeutic equity, are reviewed.

Sound promotion versus hype

The sequencing of the human genome and the tentative identification of genes' underlying susceptibility to mental disorders suggest the possibility of developing novel and more effective treatments for these disorders. Increased knowledge of the pathways for the pathophysiology of major mental illnesses can, it is hoped, lead to major therapeutic breakthroughs, the assumption being that understanding of the pathophysiological basis of these illnesses will enable the development of targeted drugs and new curative therapies.²¹

On the basis of genetic knowledge about patients' drug metabolic status, several studies recommend adjustment of therapeutic doses of antidepressants²² or antipsychotics²³ in relation to CYP2D6, CYP2C9, and CYP2C19 phenotypes. The implementation of these techniques in clinical practice—which is the ultimate goal of pharmacogenomics research in this field—can significantly improve psychiatric treatment in terms of adequate dosing, reduced side effects, averted toxic events, and improved treatment adherence and efficacy.²⁴ On the other hand, looking at the development in pharmacoge-

nomics from the perspective of earlier hopes for gene transfer-based therapies, there is a non-negligible risk that scientists and their funding agencies, as well as the pharmaceutical industry, play up or hype the possibilities.²⁵

The primary concern is with scientific adequacy. Are the scientific underpinnings of the pharmacogenomic promises sound? Do the players sufficiently acknowledge the scientific uncertainties that are connected to pharmacogenomics research; for example, the complex interactions between genes/brain/environment that underlie the development of mental disorders? In order to appreciate the significance of genetic explanations of complex and heterogeneous disorders, such as schizophrenia, eg, in terms of the genetic susceptibility for its development, it is necessary also to understand the role of epigenetic factors (heritable genomic functions that are not contained in the DNA sequence code) and factors related to the psychosocial environment.²⁶ Likewise, in order to properly assess genotype-specific psychopharmacological products, complex epigenetic interactions must be taken into account. The human brain is fundamentally a biosocial structure, and mental health throughout life depends on social as well as biological conditions.²⁷ The brain develops within a “genetic envelope,” but the evolution of its architecture is subject to important social impact, notably, through the gigantic weight of the cultural imprints epigenetically stored in our brains.²⁸ The formation of synapses is both prenatal and postnatal; it is far from complete at birth. The postnatal development of the human brain lasts considerably longer than in any other animal. The most intense development occurs during the first 2 years, but it continues to puberty and after, and the highest executive functions that are determined by the frontal lobe are not fully mature until the age of around 20.²⁹ The environment is important for this process to be efficient. If neural networks are not active, they vanish³⁰: “Use it or lose it!,” as the mantra goes. In the absence of adequate stimulation, the cerebral network suffers irreversible injury,³¹ and serious mental disorders might develop.

Genetic, epigenetic, neurophysiologic, and psychosocial explanations of mental illness are complementary; they do not stand opposed in modern psychiatry. However, a correct understanding of the interactions between these distinct perspectives in the complex causal structures underlying mental disorders and their curative therapies is hard to achieve. This is not a new challenge, specific to

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pharmacogenomics, but a classical one that is reactualized in this new context. More effective treatments for mental disorders can indeed result if drugs are developed that specifically target the genes responsible. Yet the role of genes in causing mental disorders is extremely complex, as is the connection between genotype and phenotype in drug metabolism.³² It is, for example, not possible to base high-probability predictions of drug responses on single genetic variations.³³ Whilst the possible contributions of molecular biology to psychopharmacological drug discovery are important,³⁴ they must not be overemphasized or oversimplified.³⁵

It is important and legitimate for science, health care, and the pharmaceutical industry to try to promote new ideas and new types of drugs; however, if the expectations are exaggerated this may undermine public trust³⁶ and reduce financial support in the longer perspective. This is what happened to gene therapy: “When legitimate promotion became hype, followed by very public failures of clinical trials, venture capital and government sponsors withdrew from the field. The result was that scientific research suffered, and the public and other stakeholders were left holding an empty bag of promises.”³⁷

It has been claimed that enthusiasts within the academic and business fields of pharmacogenomics are guilty of too much speculation and unsubstantiated claims.³⁸ Skeptics point not only to the scientific uncertainty concerning the promises held out, but also to exaggerations in the promised reductions in ADRs,³⁹ and to the cost:benefit ratio suggested. There are signs of hype being created, when, in 2006, the pharmaceutical industry predicted that by 2010, “the discovery and development process will take half as long as it does now, and costs per drug will fall to a quarter of the current average.”⁴⁰ It is not impossible that their prediction will come true in due course, but we are not there yet, and at the time of writing that prediction seems, at least timewise, overly optimistic.

The sociological analyses of these expectations have focused on how key actors communicate visions about future prospects of the new technology.⁴¹ These key actors represent different interests, eg, industry, government, health care providers, or patient groups. Their visions are seen as coconstructions where each actor is actively helping to shape the trajectory of an emerging promising technology.⁴² Even bioethics is suggested as a helpmate, actively recruited by pharmaceutical companies and the biotech scientific community in order to

serve as a “political broker.”⁴³ A basic message in these sociological analyses is that industry, the medical profession, and patient groups are coresponsible for producing hype, and they call for a more social-science based analysis of the science behind pharmacogenomics to obtain a more realistic view of what can actually be achieved, to unravel the interests pressing for early implementation, and to deconstruct the hype.⁴⁴ In that context, it must not be ignored that social scientists, eg, ethicists, themselves may feed on the hype and be guilty of producing it. In other words, the methods of social science should be used without, however, excluding social science as an object for scrutiny.

Cost versus benefit

The first-generation antipsychotic drug clozapine is still recommended in the UK National Institute of Health and Clinical Excellence (NICE) 2009 update to its schizophrenia guidance, but in a 2002 Press Release, NICE “recommends newer antipsychotic drugs as one of the first-line options for schizophrenia.”⁴⁵ The choice between newer and first-generation drugs depends in part on the relative benefits of the drugs and their side effects, and in part on the health care budget.

An important reason to recommend newer rather than first-generation psychopharmacological drugs is that the latter tend to have more severe side effects (eg, heart disorders such as myocarditis and cardiomyopathy, the blood disorder agranulocytosis, or tardive dyskinesia, a movement disorder that is potentially irreversible). On the other hand, the newer drugs tend to be more expensive, sometimes considerably so. Often the incremental efficacy is not very spectacular, but the tolerance is improved at a cost that is unbearable for the health care system. Hence, there is a clear health care budget issue involved in the selection of drugs.

Developing new drugs is an increasingly costly procedure.⁴⁶ The development phase can take many years and is very expensive. The testing phase needed to determine, eg, if the drug is effective, safe, and by what method and dosage it is best delivered to the organ system, can also take many years and is likewise very expensive. More and more requirements are raised by the regulatory agencies, and, of potential new medicines, few will ever reach the stage of marketing and selling—a phase that can cost even more than the preceding two combined. These factors jointly make pharmaceutical

development extremely costly, and consequently, pharmaceutical companies do what they can to recoup their outlays.

In recent years, the balance of power has shifted, and the market has become more difficult for the pharmaceutical companies, due to, for example, expiring patents, attrition in the pipelines, and the fact that governments, insurance companies, and patients increasingly dictate what kind of drugs they want, and how much they are willing to pay for them. This means that it is not just the drug makers who define the threshold of innovation, but also the health care demanders. In this situation, where the pharmaceutical industry has seen its value dwindle compared with the glory days of the 1990s, the contributions of molecular biology to drug discovery hold promise of increased profit for the pharmaceutical companies.

Concerning the cost:benefit ratio of pharmacogenomic drug development, there are profoundly different visions of the future. According to the optimistic vision, a better understanding of how different diseases function both at a molecular level and as part of a biological system might enable the industry to define diseases far more precisely, and to develop drugs that are targeted towards specific disease types, rather than making one-size-fits-all drugs focusing on symptoms shared by a range of different diseases.⁴⁷ Many new drugs will then be based on biology rather than chemistry because biologic entities are typically more predictable and less toxic than chemical entities. In the aim to “get the right drug into the right patient,”⁴⁸ human research subjects will be genotyped in clinical trials to find out likely drug responses, a development also predicted importantly to reduce the time and cost of making new drugs.

If that prediction is correct, then the cost of drug development might pose less of a problem in the case of targeted medication than in the case of one-size-fits-all drugs. Pharmacogenomic developments could thus lead to better health care without increasing the customer prices, and perhaps even reducing them. This can then be a win-win situation, where patients receive better health care whilst industry boosts its revenues.

Skeptics (amongst whom we also find some sectors of the pharmaceutical industry)⁴⁹ recommend a more cautious view, arguing that the niche products that pharmacogenomics would produce risk segmenting the market, increasing the development costs, and reducing profits. The research, argue the skeptics, will take longer than

predicted to produce clinical applications, and that the alleged cost-saving will therefore not be provided.⁵⁰

Of course, the cost:benefit ratio of new therapeutic cures may be difficult to determine in advance; yet the argument of pharmacogenomic cost-efficiency can be questioned on a general basis. The market for a genotype-specific drug is perforce smaller than that of the one type fits all variety. Even if the development process becomes more efficient, the development of highly specialized drugs that target small rather than large populations can also lead to very expensive drugs. The need for pharmaceutical companies to recoup their investments is an economic reality that can clash with the interests of health care, and it is not self-evident that the latter's concerns will outweigh the former.

Therapeutic winners versus losers

The screening of participants in clinical trials by genotype raises several ethical problems. Such stratification might lead to the unfair representation of specific groups in these trials, as well as a reduction in the number of subjects included, which could affect the study's external validity and clinical applicability.⁵¹ Even with more cost- and time-efficient clinical trials, if researchers can recruit only people with a certain genotype for the testing of a specific drug,⁵² there is a risk connected to the fact that the prospective drug is tested only on a small and genetically homogenous group. Side effects might go undetected in the case of people who do not have this genotype, which means that a drug could be marketed with less premarketing exposure and less information about adverse effects. This may not be a problem if only patients with the tested genotype use it, but if (eg, through prescription error, or nonprescribed uses) someone with a different genotype takes it, the knowledge of possible additional side effects for these people is wanting. This is different from drug errors with the randomized tested traditional drugs. In the case of the latter, if a person unjustifiably takes a nonprescribed drug, or if a psychiatrist erroneously prescribes a drug, eg, an antidepressant, the possible risks and side effects are reasonably well foreseeable, and can probably be treated if the person seeks medical assistance. If the same person erroneously takes a genotype-specific drug, there is no tested knowledge about what might happen.

This is not an argument against the development of genotype-specific drugs, but an argument for the development

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of a social infrastructure to handle their distribution. The problem highlights many challenges involved in integrating pharmacogenomic drugs into psychiatric care, eg, the need for simple and accessible pharmacogenetic tests with clinical guidelines that allow psychiatrists and health care personnel to use these tests adequately, and to prescribe or recommend pharmacogenetic drugs,⁵³ as well as the need for effective measures to prevent nonprescribed use. The genetic information obtained must also be legally safeguarded to protect privacy and confidentiality,⁵⁴ and calls for caution have been made to “regulate the use of genetic tests.”⁵⁵

A further problem remains, from the point of view of the patient, that is connected to the costs involved in targeted drug development. This concerns the fact that some people may belong to less profitable patient groups.

In order to regain the investment in a drug that is targeted towards a small population, the price must be higher than if the drug were able to be distributed to a large population. This economic principle poses a problem for so-called “orphan diseases,” ie, medical conditions that are either too rare, or that touch populations too poor for drug development in that area to be profitable. Less profitable patient groups stand a smaller chance of having remedies developed than profitable patient groups with diseases that are also prevalent in developed countries. To remedy the situation, public policies in many countries fund or facilitate research aiming to produce “orphan drugs” specifically targeted to treat these rare conditions, or these diseases that primarily haunt poor populations. Now pharmacogenomics introduces a new way of belonging to a less profitable patient group. To the traditional criteria of having a rare disease, or being burdened by poverty, we may now add having a rare genotype.

When new pharmacogenomic drugs are developed they need to be tested in specific patient groups targeted by specific drugs. However, it might be difficult to find a sufficient number of patients for a trial of rare variants of individual biomarker profiles.⁵⁶ It can also be expensive to develop a new drug for such small groups. Patients with less profitable genotypes are therefore at risk of becoming “therapeutic orphans,” and governments may need to extend their orphan drug policies to remedy this additional form of inequity.⁵⁷

If pharmacogenomic drug development enables precision in the inclusion of patients that can be helped by a

drug, it ipso facto entails the equally targeted exclusion of those that cannot. The limit between pharmacological inclusions versus exclusions can in some cases be a question of race, or ethnicity. For example, drugs to treat high blood pressure, or hypertension, have different effects on black versus Caucasian populations, as the high number of clinical trials investigating this listed on the US National Institute of Health’s Web site on clinical trials illustrates.⁵⁸ The concept “race” is scientifically controversial; some claim that “race is biologically meaningless,”⁵⁹ whereas others argue that this depends on how the concept is defined.⁶⁰ In pharmacology, it seems well established that different ethnic groups, at least, respond in different manners to drugs, which is one reason why the International Conference on Harmonization (ICH) was created to harmonize the technical requirements for registration of pharmaceuticals for human use in the three main regions: Europe, the US, and Asia. Japan has insisted that due to their ethnic pharmacological specificity, phase 1 studies must always also be done in Asian populations.⁶¹

If therapeutic (in)equity can be connected to race, or ethnicity, this is something that the social assessment of pharmacogenomic drug development needs to take into account. As the problem of orphan drugs and diseases illustrates, pharmaceutical companies have no obligation to develop drugs in an equitable manner, eg, with racial or ethnic nonbias. If a racial or ethnic group is very small, for example, the cost:benefit ratio for developing drugs to treat that group may not be economically rewarding. This is a further form of possible discrimination that governments may need to deal with in their health care and health research policies in order to ensure the protection of genetic or ethnic minorities.

Conclusion

Personalized medicine in psychiatry, eg, in the form of tailored antidepressant or antipsychotic treatment, has already made important progress, notably in terms of adjusted therapeutic doses, and predictable drug responses or drug-induced side effects. Although promising, these opportunities also give rise to numerous scientific, ethical, legal, and social challenges. An adequate assessment of personalized medicine in psychiatry must within all these perspectives be based both on analyses of the science behind pharmacogenomics research to get a realistic view of what can actually be achieved, and on

analyses of the relevant sociopolitical structures surrounding this research. Justified hopes must not be inflated to become hypes of exaggerated promises that would serve no legitimate purpose. Signs of hype, for instance in the form of pressures for rash implementation, should be forestalled and a realistic view presented. Realistic cost:benefit analyses are needed to produce reasonable health care budgets; pharmacogenetic tests must be developed together with guidelines for their use, so that the new techniques can be responsibly implemented in clinical practice; public policies on orphan diseases and drugs may need to be extended to avoid creating a new group of “genetic orphans”; whilst legal

regulations are needed to ensure that the genetic information obtained is safely protected from misuse, and that genetic or ethnic minorities are protected from discrimination.

The ethical considerations that have here been considered in terms of adequacy, cost, and therapeutic equity raise no objections to the development of personalized medicine per se in this domain. Rather, they point to the necessity of developing a social infrastructure with adequate guidelines to ensure the responsible implementation of these promising new techniques. □

Acknowledgements: I thank Marc Thomson, MD, FBCPM, for his valuable contributions and many helpful comments to this article.

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La medicina personalizada en psiquiatría: oportunidades y desafíos éticos

Los progresos farmacogenómicos generan esperanzas para la medicina personalizada dentro de la psiquiatría en cuanto a ajuste de dosis terapéuticas, respuestas predecibles, reducción de las reacciones adversas a los fármacos, diagnóstico precoz y programas personales de salud. Las posibilidades son apasionantes, pero al mismo tiempo estas nuevas técnicas se enfrentan con importantes desafíos científicos, éticos, legales y sociales, los que requieren estar de acuerdo con los avances científicos para que ellas se puedan aplicar responsablemente. Esta revisión discute el balance ético entre los desafíos y oportunidades de la medicina personalizada en psiquiatría en relación con aspectos de adecuación, relación costo beneficio y equidad terapéutica. Se argumenta que el carácter prometedor de estas alternativas terapéuticas hace aun más importante evitar la exageración de las expectativas y que se necesita desarrollar una sofisticada infraestructura social para asegurar la aplicación realista y responsable de la medicina personalizada en psiquiatría.

Médecine personnalisée en psychiatrie : opportunités et défis éthiques

Les développements de la pharmacogénomique ont tenu leurs promesses pour la médecine personnalisée en psychiatrie en permettant d'ajuster les doses thérapeutiques, de prévoir les réponses, de diminuer les effets indésirables, d'établir des diagnostics précoces et des calendriers personnels de santé. Les perspectives sont prometteuses mais en même temps, ces nouvelles techniques doivent faire face à des défis scientifiques, éthiques, légaux et sociaux importants afin de permettre aux avancées scientifiques de s'appliquer de manière responsable. L'équilibre éthique entre défi et opportunité de la médecine personnalisée en psychiatrie fait l'objet ici d'une discussion au sujet de sa pertinence, de son rapport coût/bénéfice, et de son équité thérapeutique. La nature prometteuse de ces possibilités thérapeutiques prend le pas sur le risque d'attentes exagérées ; la mise en application réaliste et responsable de la médecine personnalisée en psychiatrie demande de développer une infrastructure sociale sophistiquée.

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A new paradigm for the prediction of antidepressant treatment response

Andrew F. Leuchter, MD; Ian A. Cook, MD; Aimee M. Hunter, PhD; Alexander S. Korb, BS



The current treatment paradigm for Major Depressive Disorder

Major Depressive Disorder (MDD) is a significant public health problem. The annual costs of depression are estimated at 83.1 billion US dollars.¹ Nearly two thirds of this cost comes from impaired productivity and

Current treatment of Major Depressive Disorder utilizes a trial-and-error sequential treatment strategy that results in delays in achieving response and remission for a majority of patients. Protracted ineffective treatment prolongs patient suffering and increases health care costs. In addition, long and unsuccessful antidepressant trials may diminish patient expectations, reinforce negative cognitions, and condition patients not to respond during subsequent antidepressant trials, thus contributing to further treatment resistance. For these reasons, it is critical to identify reliable predictors of antidepressant treatment response that can be used to shorten or eliminate lengthy and ineffective trials. Research on possible endophenotypic as well as genomic predictors has not yet yielded reliable predictors. The most reliable predictors identified thus far are symptomatic and physiologic characteristics of patients that emerge early in the course of treatment. We propose here the term "response endophenotypes" (REs) to describe this class of predictors, defined as latent measurable symptomatic or neurobiologic responses of individual patients that emerge early in the course of treatment, and which carry strong predictive power for individual patient outcomes. Use of REs constitutes a new paradigm in which medication treatment trials that are likely to be ineffective could be stopped within 1 to 2 weeks and other medication more likely to be effective could be started. Data presented here suggest that early changes in symptoms, quantitative electroencephalography, and gene expression could be used to construct effective REs. We posit that this new paradigm could lead to earlier recovery from depressive illness and ultimately produce profound health and economic benefits.

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Dialogues Clin Neurosci. 2009;11:435-446.

Keywords: major depression; antidepressant medication; predicting treatment response; antidepressant treatment response (ATR) index; response endophenotype

Author affiliations: Laboratory of Brain Behavior, and Pharmacology, and the Depression Research and Clinical Program, Semel Institute for Neuroscience and Human Behavior at UCLA, and the Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

Address for correspondence: Andrew F. Leuchter, MD, Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior at UCLA, 760 Westwood Plaza, Los Angeles, CA 90024, USA (e-mail: afl@ucla.edu)

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absenteeism from work. Approximately 14.8 million American adults² (6.7% of the population) suffer from MDD, and cost employers more than \$44 billion per year in lost productive time and 387 million days per year of disability.¹ While the economic costs are substantial, the personal costs of prolonged suffering are incalculable.

The costs of MDD are high, in part because it takes so long for patients with MDD to recover from the illness. Even after 1 year of treatment with enhanced resources under a structured algorithm, only 11% of patients achieved remission.³ This low recovery rate is not simply a matter of needing more or better medications. There are more than 20 treatments for MDD approved as effective by the Food and Drug Administration (FDA). The challenge is choosing the best treatment for each patient. The current treatment guidelines for MDD of the American Psychiatric Association⁴ support a “watchful waiting” approach to determine if a particular medication will be useful for an individual patient. In order to determine whether a medication will lead to response ($\geq 50\%$ reduction in depressive symptoms) or remission (nearly complete resolution of symptoms), it is recommended that a physician wait to see if it will be effective.⁴ On average, at least 4 weeks are needed to attain response and 6 weeks to attain remission during treatment with an initial selective serotonin reuptake inhibitor (SSRI) antidepressant; in a number of cases, however, remission can take 12 weeks or longer to attain.⁵ In practice, physicians commonly wait 6 to 8 weeks to determine if a patient will recover with whichever medication is chosen.^{6,7}

It is not surprising that, under the current treatment paradigm, most patients face a long and frustrating course of treatment. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the largest study of MDD conducted in the United States, showed that even with enriched resources devoted to treatment, recovery with the first selected SSRI occurred only about 30% of the time.⁸ More than 20% of those who failed to improve with the first treatment simply stopped taking medication, primarily within the first 2 weeks.⁹ Although medication may take up to 12 weeks to be effective, 42% of patients discontinue medication within the first 30 days.¹⁰ A high proportion of the patients who prematurely stop treatment are from ethnic minority groups,¹⁰ and this may contribute to the significantly poorer clinical outcomes observed among ethnic minority patients.¹¹

Failure to respond to treatment at any one step is commonly followed by “sequential treatment” in which a subsequent treatment is utilized either alone in combination,¹²⁻¹⁴ followed by another period of watchful waiting. In most studies, only about 15% of patients will ultimately fail to benefit from sequential medication treatment, but it may take 1 to 2 years to identify the treatment that will get a patient well—and many discontinue treatment before they can recover.¹⁵ For those individuals who leave treatment prematurely, suffering, disability, impaired productivity, and absenteeism from work may continue indefinitely. For those who remain in treatment, the delay in recovery from MDD increases health care costs. While they are depressed, patients with MDD have at least a 50% increase in total health care costs for general medical conditions.¹⁶

The current paradigm of watchful waiting is seriously flawed. Lengthy medication trials determine with a high degree of certainty whether a particular medication will be effective. Because only a minority of patients will recover with any one medication, however, this paradigm prolongs the length of depressive episodes for most patients, increases health care costs, and increases the likelihood that many patients will drop out and never receive adequate treatment. The approach of lengthy medication trials essentially sacrifices the health of the majority of patients for the certainty of knowing whether a particular antidepressant will be effective.

Limitations of the current treatment paradigm

In sequential treatment, subsequent antidepressant medications commonly are selected based upon their putative mechanism of action (MOA), with medications that have a different MOA usually given preference.¹⁷ It has never been shown, however, that MOA is related to effectiveness in switching or combining medications.¹⁸ The results from level II treatment in STAR*D suggested that patients respond or remit to different antidepressants at similar rates, regardless of the MOA.^{19,20} The sole reliable predictor of improvement in sequential treatment is that improvement at one step is associated with further improvement at the next step, whereas failure to improve indicates a poor prognosis for improvement during future treatments.^{19,21} The STAR*D study demonstrated that each subsequent medication trial was less and less likely to be effective

for patients with unsatisfactory response at the previous level.^{13,19,21-23}

The development of increasing resistance over the course of antidepressant treatment is well established but not well understood. It largely has been interpreted as representing the fact that those who fail to benefit from adequate trials of earlier treatments are simply predisposed not to respond to multiple treatments, sometimes because of comorbid conditions.²⁴ This hypothesized process through which successive treatment failures identify and isolate an increasingly treatment-resistant population may account, at least in part, for the escalation in failure rates with successive trials. This “distillation” hypothesis, however, is unlikely to account fully for increasing treatment resistance with multiple antidepressant trials. Even within a trial of a single antidepressant medication, there is a great deal of heterogeneity in onset of improvement that is not easily explained by commonly measured clinical features. Half of patients require more than 6 weeks to enter remission and a significant number of patients still enter remission up to 12 weeks, yet these later remitters eventually may attain a degree of improvement comparable to those who enter remission rapidly.⁵

A number of factors are likely to affect speed and completeness of medication responsiveness. Whereas some of these factors may reflect heritable or constant biological factors, others may be more dynamic and represent the state of the individual at the specific time that he or she enters treatment.²⁵⁻²⁷ Many such intraindividual factors are psychological, including patient expectations, cognitions, or conditioned responses. Data from subjects enrolled in clinical trials has shown that patients with high expectations of the effectiveness of their treatment are more likely to benefit from their treatment,^{28,29} and to respond more rapidly.²⁹ Patients who are uncertain about the benefit of their antidepressant treatment may even discontinue medication before it has had time to work.³⁰ These findings are consistent with the fact that in the setting of a placebo controlled trial, patients' certainty that they will be receiving the active medication as compared with placebo is directly related to their likelihood of response. Patients who are informed that they have a 50% likelihood of receiving active medication are significantly more likely to respond than those who are informed that their probability of receiving medication is only 20%.³¹ It is reasonable to postulate that anything in the treatment set-

ting that alters patients' expectations of improvement is likely to alter their likelihood of benefiting from a medication. Insofar as prolonged prior administration of an ineffective antidepressant may diminish expectations of improvement, this practice may contribute to the failure of subsequent trials.

Cognitive theories of depression suggest that, in the context of dysfunctional attitudes that subserve depression, failed treatment attempts would perpetuate negative thoughts and contribute to future failures. Beck's cognitive theory postulates that dysfunctional attitudes develop in response to specific stressors in the midst of an episode of depression.³² The poorer treatment outcomes of some depressive subtypes is partly explained by the patients' level of negative or dysfunctional cognitions.³³ Depressed patients' interpretation of negative events also may increase the likelihood of maintaining depression and of poor response to medication.^{34,35} In the midst of an episode of MDD, ineffective treatment trials may constitute a specific stressor that, interpreted in a negative context, could combine with dysfunctional attitudes to result in increasingly resistant depression in some patients.

Classical conditioning also may play a role in antidepressant resistance during successive trials. Animal models have shown that pharmacologic responses to a number of different therapeutic agents can be classically conditioned,^{36,37} including responses to antidepressant agents.³⁸ Similarly, pharmacologic nonresponse can also be conditioned to a reuptake inhibitor drug.³⁹ A related concept in the classical conditioning paradigm is the process of latent inhibition, in which frequent administration of a cue (in this case, antidepressant pill-taking) that is not associated with a significant outcome prevents future conditioning to that cue.⁴⁰ There is evidence to suggest that patients' physiologic responses to antidepressant medications are in part conditioned responses. A number of brain imaging studies have shown that effective antidepressant treatment is associated with decreases in metabolism or brain electrical activity in the prefrontal cortex.^{41,42} While these changes in function appear to be associated with antidepressant treatment, brain imaging during a placebo lead-in showed that the changes thought to be associated with successful antidepressant treatment actually preceded administration of the medication.²⁵ These findings suggest that a psychological process such as conditioning plays a role in eliciting brain functional changes. Whether nonresponse

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to pharmacotherapeutic agents can be conditioned in the clinical setting by prolonged nonresponse to antidepressants has not been established.

It is difficult to demonstrate the role of expectations, cognitions, or conditioned responses in the failure to respond to successive antidepressant medication trials in humans. It is known that administration of an antidepressant is less effective after the patient has received no benefit from either a first antidepressant²¹ or a placebo,⁴³ but multiple crossover trials would be necessary to determine the mechanism for this loss of effectiveness. There is clearer evidence from human pain studies, however, that ineffective medication trials directly contribute to decreases in the effectiveness of subsequent analgesic medications. The effectiveness of an analgesic medication is degraded when administered after an ineffective dose of medication or placebo; furthermore, the more doses of the ineffective compound that are given, the less likely that the analgesic will have a therapeutic effect.^{44,45} Blinded administration of effective analgesics also diminishes their effectiveness.⁴⁶ Expectations, conditioning, and cognitive factors all have been shown to be involved in mediating these effects.^{46,47}

In summary, unsuccessful antidepressant trials may diminish patient expectations, reinforce negative cognitions, and condition patients not to respond during subsequent antidepressant trials. Regardless of the psychological mechanism, the above theories and data suggest that ineffective medication trials may, in and of themselves, predispose patients to experience diminished medication effectiveness in future trials.

The state of endophenotypic and genomic predictors

There are several strategies that could be employed to overcome the shortcomings of the current paradigm for prescribing antidepressant medications. One of these would be to identify, prior to treatment, the medication that has the highest likelihood of benefitting the patient. Research has sought to identify “endophenotypes” that could predict response or remission to specific antidepressants for individual patients. As defined by Gottesman and Gould,⁴⁸ an endophenotype must meet five criteria:

1. The endophenotype is associated with illness in the population.
2. The endophenotype is heritable.

3. The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active).

4. Within families, endophenotype and illness cosegregate.

5. The endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population.

Endophenotypes thus are measureable characteristics or physiologic indices that fill “the gap between available descriptors and between the gene and the elusive disease process.”⁴⁹ Exhaustive studies of clinical features, family history, as well as sleep patterns and neuroendocrine correlates, have identified general prognostic indicators for treatment outcome for depression.^{50,51} In some cases, the predictors may be useful for groups of patients with certain subtypes of depression (ie, psychotic depression).⁵² While some symptomatic and physiologic features in MDD patients demonstrate promise as putative endophenotypes, many do not fulfill the actual criteria for an endophenotype or meet the goal of providing greater prognostic specificity than the definition of the illness itself.⁵³ Some brain imaging findings also have demonstrated prognostic significance⁵⁴⁻⁵⁷ and may fulfill the criteria for an endophenotype.⁵⁸ Part of the challenge in identifying true endophenotypes in MDD is that the physiologic and genetic underpinnings of MDD are complex and poorly understood. As a result, imaging findings may reflect confounds such as interindividual heterogeneity in brain structure or function unrelated to illness, or the effects of previous or concomitant medication treatment.⁵⁸ No clinically meaningful endophenotypes predictive of response to specific medications in individual patients prior to the start of treatment yet have been identified.^{59,60}

An alternative to the endophenotypic approach has been to examine genetic polymorphisms as possible outcome predictors. Recent studies have suggested that common genetic variations may be associated with response to specific antidepressant medications.⁶¹⁻⁶³ For example, some common polymorphisms in serotonin system genes have been shown to influence the outcome of SSRI treatment.^{62,64} Many of these results have not consistently replicated or do not allow the estimation of prediction accuracy in a clinical population.⁶⁵ The relative lack of reproducibility in pharmacogenetic studies may reflect the fact that the contributions of individual polymorphisms may be small and, therefore, large pop-

ulations may be needed to detect the effect.⁶⁶ Given the complexity of influences “downstream” from genotype,⁶⁴ genotype alone may be insufficient to capture the state of those systems that subserve antidepressant action in an individual patient. To date, research on possible genomic factors has not yet yielded reliable predictors.

Response endophenotypes

The most reliable treatment response predictors identified thus far are symptomatic and physiologic characteristics of patients that emerge early in the course of treatment. We propose here the term “response endophenotypes” to describe this class of predictors. Specifically, we define response endophenotypes (REs) as latent measurable symptomatic or neurobiologic responses of individual patients that emerge early in a course of treatment and which carry strong predictive power for individual patient outcomes. In some diseases, endophenotypic characteristics are elicited by a physiologic challenge (ie, glucose tolerance tests, stress electrocardiography).^{53,67} The distinction of the term response endophenotype is that it describes a class of markers that are *exclusively* observed in response to specific *treatment* challenges. Although there is evidence that response to medication is at least in part genetically mediated, it is not firmly established that the REs presented below necessarily are heritable. It is therefore appropriate to consider REs as putative endophenotypes, pending research to establish heritability and fulfillment of the other characteristics of an endophenotype.⁴⁸

In the prediction of treatment response in MDD, there are significant advantages to composing endophenotypes exclusively from measureable changes in an individual in response to a specific treatment. First, the fact that these characteristics are measured “within subjects” likely enhances stability, statistical reliability, and therefore predictive accuracy of the measures. Preliminary data presented below suggest that use of REs may facilitate prompt and accurate matching of patients with the medication most likely to benefit them. Second, the fact that RE components are measured in response to newly administered treatments may overcome some of the confounding factors inherent in the development of conventional endophenotypes in MDD. It is problematic to derive prognostic significance from static, cross-sectional measures in MDD patients; such measurements are

inevitably affected by the number and severity of prior episodes, the current phase of illness, and the extent and types of prior and current treatment.⁵⁸ Examination of dynamic measures specific to the current treatment may detect features that are common across individuals who will respond to the treatment, irrespective of confounding factors. There are three broad classes of measures that may change within the first 48 hours to 2 weeks of treatment that have been identified thus far as potential predictors of treatment response or remission, and therefore may be useful as components of an RE. Each of these is discussed separately below.

Early changes in depressive symptoms

The average time to response in treatment with a prototypical SSRI is 1 month, and to remission is 6 weeks.⁵ While some patients continue to enter remission up to 12 weeks or even longer after the initiation of treatment, the time to symptomatic *improvement* is much shorter. Many patients, particularly those with milder symptoms, show improvement (defined by at least a 20% decrease in depressive symptoms) within the first 2 weeks of treatment.⁶⁸⁻⁷¹ Although some have suggested that early response is likely to represent a placebo response,^{72,73} early response is in fact twice as likely with medication as with placebo.⁷¹

The largest meta-analytic study of this topic was performed by Szegedi and colleagues,⁷⁴ who examined 6562 subjects treated primarily with mirtazepine, but also with SSRIs, tricyclic antidepressants (TCAs), and venlafaxine. These investigators found that more than 50% of patients had at least a 20% improvement in depression rating scores by the end of 2 weeks of treatment. Of those who did not show early improvement, only 11% and 4.1% showed eventual response and remission, respectively. Early improvement was a highly sensitive predictor of stable response (81% to 98%) or stable remission (87% to 100%), and so was a positive prognostic sign. However, the usefulness of early symptom improvement was limited by the poor specificity for stable response (43% to 60%) or remission (19% to 28%). The results of all of these studies are difficult to evaluate because they come from placebo-controlled treatment trials of selected study populations. It is clear that early symptom improvement is a positive prognostic sign, and the absence of early improvement is a negative prognostic sign. The poor specificity of the finding, how-

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ever, makes it difficult to make treatment decisions based solely upon early symptom improvement; absence of early improvement by itself is insufficiently powerful evidence to prompt a change in treatment. It is possible that early symptom changes could form part of the basis for REs to reliably predict response and remission to the specific medication that the patient receives within the first 2 weeks of treatment.

Early changes in brain electrical activity

One biomarker that has shown promise as a predictor of treatment response is quantitative electroencephalography (QEEG). Prefrontal QEEG power⁷⁵⁻⁷⁷ may identify patients who are most likely to respond to all major antidepressant medication classes. Research has shown

that QEEG changes in the prefrontal region may reliably identify antidepressant medication responders within the first 48 hours to 1 week of treatment.^{42,78} These findings are consistent with the fact that rhythmic midline prefrontal EEG activity has been shown to reflect the activity of anterior cingulate and midline prefrontal cortex,⁷⁹ brain areas implicated in mood regulation and the pathogenesis of depression.

Based upon these previous results, a multisite study was designed to test the usefulness of QEEG as a predictor. The BRITE-MD study (“Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression,” NCT00289523), examined for the first time the usefulness of a new putative neurophysiologic biomarker for medication response and remission, the Antidepressant Treatment Response (ATR) index.⁸⁰

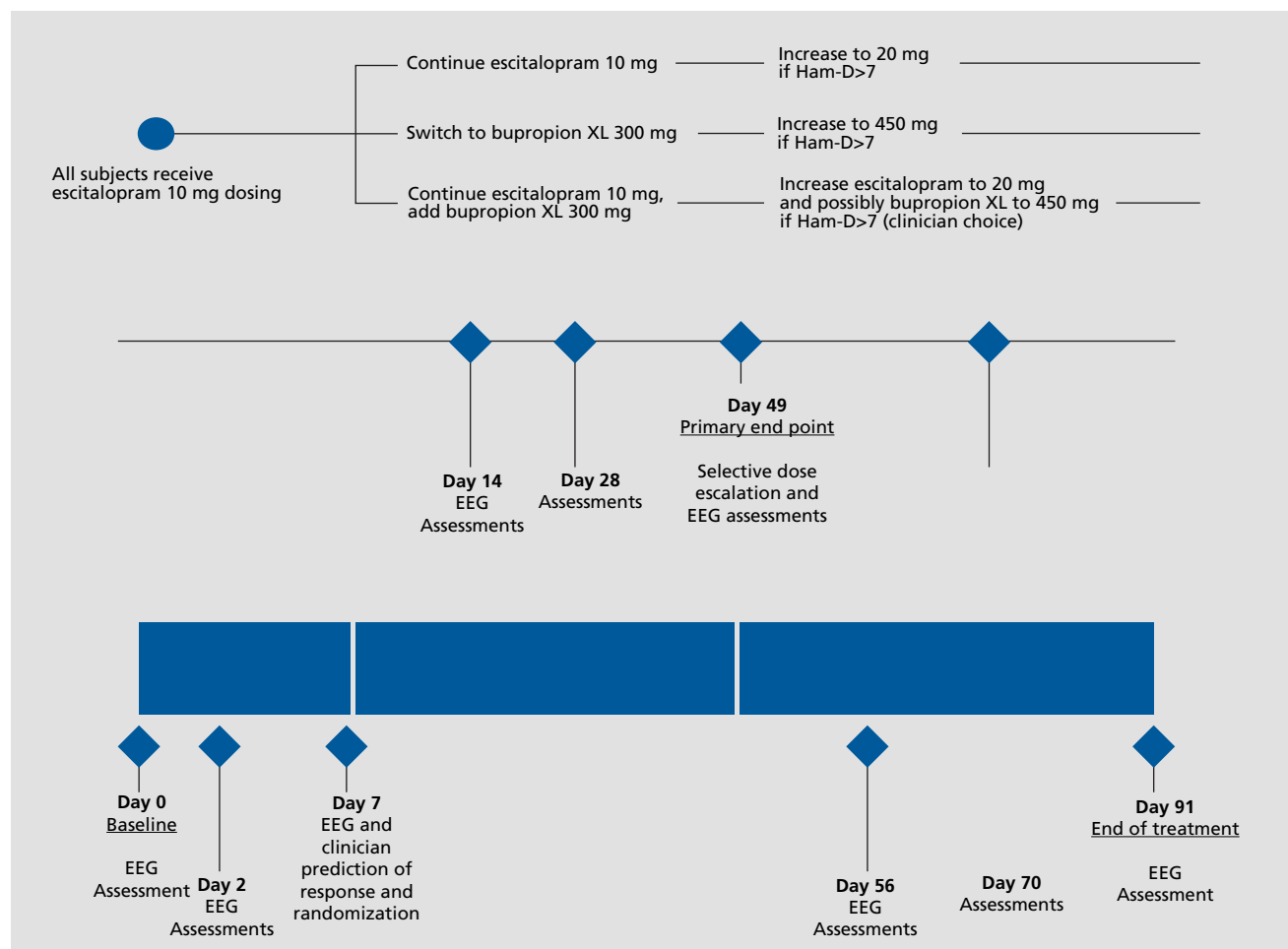


Figure 1. Study flow chart. Ham-D, Hamilton Depression Rating Scale; SSRI, selective serotonin reuptake inhibitor; EEG, electroencephalography

ATR is based upon QEEG data collected on two occasions, at pretreatment baseline (immediately before medication is started) and at the end of 1 week of treatment with medication. ATR is based upon alpha and theta band features of frontal brain electrical activity integrated and scaled from 0 (low probability of response or remission to the medication) to 100 (high probability). BRITE-MD is the largest single study of any type of neurophysiologic biomarker in MDD undertaken to date ($N=375$). All subjects were treated with an initial 1 week of escitalopram 10 mg, during which time ATR was calculated. Subjects then were randomized either to continue escitalopram, switch to bupropion, or receive a combination of the two medications (Figure 1).

The outcome measure was the Hamilton Depression Rating Scale (Ham-D₁₇) score at week 7, with response defined as a 50% decrease from the baseline score and remission defined as a final score ≤ 7 . Other putative predictors examined in BRITE included other biomarkers (serum drug levels, as well as serotonin transporter [5-HTTLPR] and postsynaptic serotonin receptor [5-HT_{2a}] genetic polymorphisms), early changes in symptoms (measured with the Ham-D₁₇ at 1 week), and clinician prediction of the likelihood of response (using a clinical global impression measure at 1 week).

The Receiver Operating Characteristic (ROC) curve for predictive accuracy of ATR with escitalopram is shown in Figure 2. An optimal threshold was chosen on this curve (58.6) to maximize accuracy in predicting response, with values above this threshold designated as a "positive" ATR and those below the threshold as "negative."

A positive ATR biomarker predicted response and remission to treatment in the escitalopram arm with high accuracy. ATR values predicted response with 74% overall accuracy, 58% sensitivity, 91% specificity, 88% positive predictive accuracy, and 67% negative predictive accuracy. ATR also predicted remission with 74% overall accuracy, 61% sensitivity, 82% specificity, 68% positive predictive accuracy, and 77% negative predictive accuracy. Neither serum drug level nor genetic polymorphisms were significant predictors of response or remission with escitalopram. Responders at week 7 had significantly larger decreases than nonresponders in Ham-D₁₇ scores at day 7 ($P=0.005$), although remitters did not. Clinician prediction based upon global impression of improvement at day 7 did not predict final outcome. Logistic regression showed that ATR and early Ham-D₁₇ changes were addi-

tive predictors of response, but ATR was the sole significant predictor of remission.⁸⁰

Another goal of BRITE was to examine the prognostic significance of a negative biomarker. The overall response rate to escitalopram in the study was 52%, but in those with a positive ATR biomarker, the response rate was 61%. Conversely, in those with a negative ATR biomarker, the response rate to escitalopram was only 28%. Analyses showed that a low ATR value predicted not only nonresponse to escitalopram, but also subsequent response to treatment among those subjects who were randomly assigned to receive the antidepressant bupropion. Subjects with ATR values above the threshold were more than 2.4 times as likely to respond to escitalopram as those with low ATR values (68% vs 28%, $P=.001$). Subjects with ATR values below the threshold who were switched to bupropion treatment were 1.9 times as likely to respond to bupropion alone than those who remained on escitalopram treatment (53% vs 28%, $P=.034$, Figures 3 and 4).⁸¹

These differences were statistically significant. One measure of the potential impact of the use of the ATR biomarker is the "number needed to treat" (NNT), namely the number of patients to whom such a test would need to be applied in order to realize one improved patient outcome.^{82,83} These results equate to a NNT of 10 to 11,

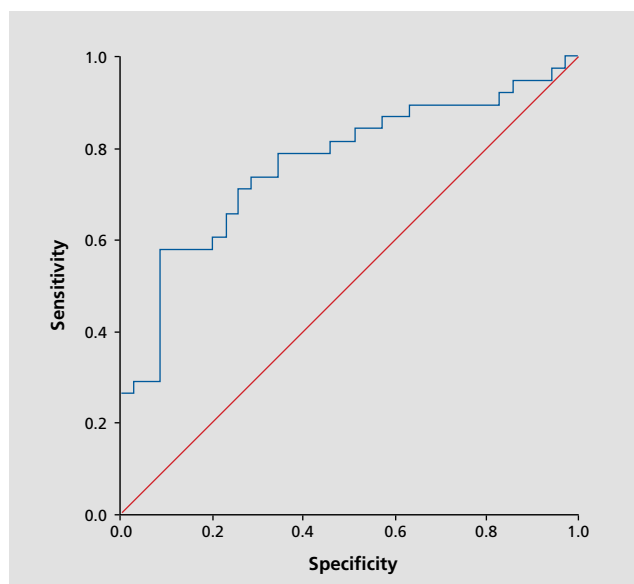


Figure 2. Receiver Operating Characteristic curve for ATR prediction of response to escitalopram treatment. ATR, Antidepressant Treatment Response index

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which is in the range that has been considered to be clinically significant.⁸⁴ These results must be interpreted with the caveat that treatment was not assigned prospectively on the basis of ATR values.

These results are encouraging, and suggest that ATR may be useful as a component of a RE for predicting early in the course of treatment which medication will be most helpful to an individual patient with MDD. The fact that ATR data appear to be complementary to early changes in depression rating scores suggests that a RE model that integrates symptom and neurophysiologic measures may be the most useful.

Gene expression markers

Some of the more intriguing putative biomarkers for antidepressant treatment response are early changes in gene expression. Animal and cell culture research, as well as study of postmortem human brains, indicates that reg-

ulation of gene expression represents a major component of the mechanism of action of available antidepressants. The expression of a host of gene families are altered by antidepressant treatment, including those for trophic factors that promote cell proliferation, growth, and resiliency (BDNF, FGF, and VEGF), cell signaling pathways, and pathways for neurotransmitter transport and metabolism, among others.^{85,86}

Because direct examination of gene expression in patients' brains is impractical, recent research has examined gene expression in peripheral leukocytes, which share identical genetic material and may exhibit similarly altered expression in response to antidepressant medications. There have been limited small previous studies of gene expression through leukocyte mRNA in response to antidepressant or lithium treatment in patients with MDD or bipolar disorder.⁸⁷⁻⁹³ These studies have confirmed and extended research from animals, showing significant differences prior to treatment between bipolar

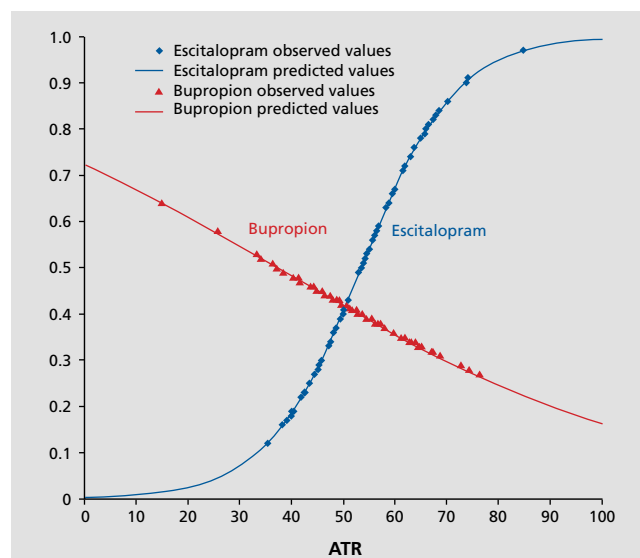


Figure 3. Logistic regression models of escitalopram and bupropion responders stratified by ATR values. ATR values of subjects randomly assigned to each treatment and who responded to escitalopram or bupropion treatment. Subjects who responded to escitalopram (blue) tended to have higher ATR values, and those who responded to bupropion (red) tended to have lower ATR values. Markers represent observed values and lines represent modeled values. ATR, Antidepressant Treatment Response index

Adapted from ref 81: Leuchter AF, Cook IA, Gilmer WS, et al. Effectiveness of a quantitative electroencephalographic biomarker for predicting differential response or remission with escitalopram and bupropion in Major Depressive Disorder. *Psychiatry Res.* 2009;169:124-131. Copyright © Elsevier, 2009

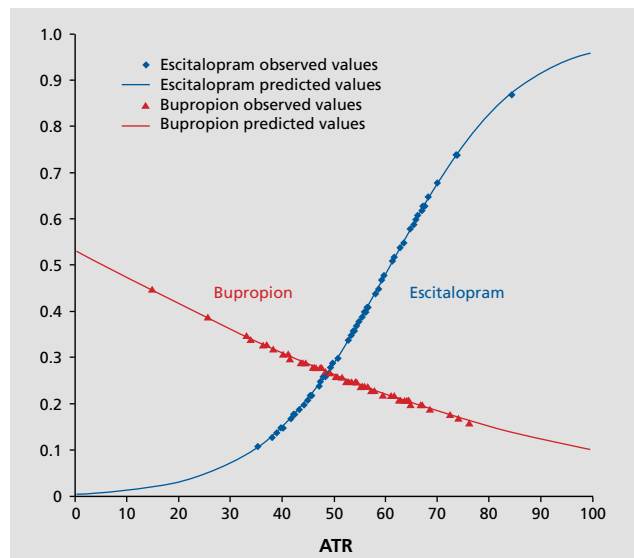


Figure 4. Logistic regression models of escitalopram and bupropion remitters stratified by ATR values. ATR values of subjects randomly assigned to each treatment and who remitted with escitalopram or bupropion treatment. Subjects who remitted with escitalopram (blue) tended to have higher ATR values, and those who remitted with bupropion (red) tended to have lower ATR values. Markers represent observed values and lines represent modeled values. ATR, Antidepressant Treatment Response index

Adapted from ref 81: Leuchter AF, Cook IA, Gilmer WS, et al. Effectiveness of a quantitative electroencephalographic biomarker for predicting differential response or remission with escitalopram and bupropion in Major Depressive Disorder. *Psychiatry Res.* 2009;169:124-131. Copyright © Elsevier, 2009

or MDD subjects and normal controls in expression of trophic and transcriptional factors, as well as cell signaling proteins. In some small studies, antidepressant treatment tended to normalize gene expression patterns and the degree of normalization was proportional to the degree of symptom improvement.^{90,92} No study has utilized microarray-based screening of large numbers of expressed genes to predict treatment response in MDD, but one study has performed such screening in a small number of subjects with juvenile epilepsy and identified patterns of change in expression that accurately differentiated subjects who were seizure-free on valproate from those who were not.⁹⁴

Because of limited research in this area, the gene expression approach is highly speculative. Furthermore, the biological basis through which gene expression changes measured in peripheral blood reflect the central effectiveness of medications admittedly is not fully clear. There are several possible mechanisms including: i) parallel expression changes in the brain and peripheral blood; ii) leukocyte responses to change in the brain; iii) responses of the leukocytes to a change in the physiological state of the subject; and/or iv) changes in the composition of the leukocyte population. Regardless of the mechanism, sufficient data exist to support the plausibility of testing the use of gene expression in peripheral leukocytes to predict clinical responsiveness to antidepressants. Expression profiles could potentially be applied in the clinic to aid in the treatment of MDD, and because the fundamental measure is the *change in gene expression* within a patient between two time points, each patient acts as his or her own control, greatly reducing the artifacts that could arise from directly comparing gene expression across unmatched subjects, such as subject-to-subject expression differences due to extraneous factors such as ethnicity, gender, age, or environment factors.

Conclusion

The use of REs for predicting antidepressant treatment response and remission has the potential to overturn a

flawed biomedical paradigm that forms the basis for clinical research and treatment in MDD, namely, the long empiric medication trial. Fewer than half of patients respond to treatment under this paradigm, and fewer than one third recover. This paradigm leads to prolonged suffering and increased health care costs. If we were successful in identifying response endophenotypes for patients with MDD, medications would be prescribed under an entirely new paradigm that relied upon an early response profile of each patient. The concept of the response endophenotype shifts from the examination of endophenotypes and genotypes, which have not proved highly productive, to the study of dynamic treatment-emergent characteristics. In this paper we have suggested early changes in symptoms, brain neurophysiology, and patterns of changes in gene expression as potential REs. The RE concept need not be limited, however, to these few measures. Any early treatment-emergent measures that could be examined within the individual patient could be incorporated in this paradigm. We posit that this paradigm could optimize response and remission rates with medication and prove superior to the current approach, leading to earlier symptom improvement, recovery from the illness, and ultimately profound health and economic benefits in terms. □

Acknowledgements: Financial support of this project was provided by a grant from the National Institute on Mental Health (R01 MH 085925) and by an endowment in depression research from Joanne and George Miller and Family (Dr Cook), and by NIH Training Grant T32 MH017140 (Mr Korb).

Andrew Leuchter, MD, has provided scientific consultation or served on advisory boards for Aspect Medical Systems, Eli Lilly and Company, Novartis Pharmaceuticals, MEDACorp, AstraZeneca, Takeda Pharmaceuticals, and Merck & Co. He has served on a speaker's bureau for Eli Lilly and Company and Wyeth-Ayerst Pharmaceuticals. He has received research/grant support from the National Institute of Mental Health, the National Center for Complementary and Alternative Medicine, Aspect Medical Systems, Eli Lilly and Company, Novartis Pharmaceuticals, Wyeth-Ayerst Pharmaceuticals, Merck & Co, Pfizer, Vivometrics, and MedAvante.

Ian A. Cook, MD, has served as an advisor and consultant for Ascend Media, Bristol-Myers Squibb, Cyberonics Inc, and Janssen. He has served on the Speaker's Bureau for Bristol-Myers Squibb, Medical Education Speakers Network, Pfizer Pharmaceuticals Inc, and Wyeth Pharmaceuticals. Dr Cook receives Research Support from Aspect Medical Systems, Cyberonics Inc, Eli Lilly & Company, Novartis Pharmaceuticals, Pfizer, Inc, and Sepracor.

Dr Hunter and Mr Korb have nothing to disclose.

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Un nuevo paradigma para predecir la respuesta al tratamiento antidepresivo

El tratamiento actual del trastorno depresivo mayor emplea una estrategia terapéutica secuencial de ensayo-error que se traduce en demoras para alcanzar la respuesta y remisión para la mayoría de los pacientes. El tratamiento ineficaz prolongado alarga el sufrimiento del paciente y aumenta los costos de salud. Además, los ensayos prolongados e ineficaces con antidepresivos pueden disminuir las expectativas del paciente, reforzar las cogniciones negativas y condicionar a los pacientes a no responder durante los siguientes ensayos con antidepresivos, contribuyendo así a una resistencia a posteriores tratamientos. Por estas razones, es fundamental identificar predictores confiables de la respuesta al tratamiento antidepresivo que puedan utilizarse para abreviar o eliminar los ensayos prolongados e ineficaces. La investigación tanto de posibles endofenotipos como de predictores genómicos aun no ha entregado predictores confiables. Los predictores más confiables que se han identificado hasta ahora son ciertas características sintomáticas y fisiológicas de los pacientes, las que aparecen precozmente durante el curso del tratamiento. Aquí se propone el término «respuesta endofenotípica (RE)» para describir esta clase de predictores, definidos como respuestas precoces y latentes tanto sintomáticas como neurobiológicas que se pueden medir en cada paciente y que tienen un alto poder predictor para la evolución clínica individual. El empleo de la RE constituye un nuevo paradigma para los ensayos de tratamientos medicamentosos que tengan una alta probabilidad de ser inefectivos, ya que éstos podrían ser suspendidos dentro de una o dos semanas para dar inicio a otra medicación con mayor probabilidad de ser eficaz. Los datos aquí presentados sugieren que los cambios precoces en los síntomas, en la electroencefalografía cuantitativa y en la expresión génica podrían ser utilizados para construir REs efectivas. Se postula que este nuevo paradigma podría llevar a recuperaciones más precoces de la enfermedad depresiva y a la larga producir marcados beneficios de salud y económicos.

Un nouveau paradigme de prédiction de la réponse au traitement antidépresseur

Une stratégie thérapeutique séquentielle par essais/erreurs est actuellement utilisée dans le traitement du trouble dépressif majeur entraînant une réponse et une rémission retardées pour la majorité des patients. Un traitement inefficace prolongé allonge la souffrance du patient et augmente les coûts des soins de santé. De plus, des séquences thérapeutiques longues et infructueuses par antidépresseurs contribuent à diminuer les attentes des patients, à renforcer les opinions négatives et conditionnent les patients à ne pas répondre au cours des traitements ultérieurs, contribuant ainsi à une résistance. Il est donc crucial pour ces raisons d'identifier des prédicteurs fiables de la réponse au traitement antidépresseur, pour raccourcir ou éliminer les séquences thérapeutiques très longues et inefficaces. La recherche sur des facteurs prédictifs endophénotypiques ou génomiques possibles n'est pas encore fiable. Les facteurs prédictifs les plus fiables identifiés jusqu'à maintenant sont des caractéristiques symptomatiques et physiologiques des patients apparaissant précocement au cours du traitement. Nous proposons ici le terme « d'endophénotypes de la réponse » (ER) pour décrire cette classe de prédicteurs, définis comme des réponses précoces latentes symptomatiques ou neurobiologiques mesurables pour chaque patient, avec un pouvoir prédictif de l'évolution clinique de chacun. L'utilisation des ER constitue un nouveau paradigme dans lequel les séquences thérapeutiques de traitements risquant d'être inefficaces pourraient être arrêtées dans les 1 à 2 semaines, laissant place à d'autres antidépresseurs probablement plus efficaces. Les données présentées suggèrent que les modifications précoces des symptômes, l'électroencéphalographie quantitative et l'expression des gènes pourraient être utilisés pour bâtir des ER efficaces. Nous postulons que ce nouveau paradigme pourrait conduire à une guérison précoce de la maladie dépressive et finalement apporter des bénéfices économiques et de santé profonds.

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Prevention: an achievable goal in personalized medicine

Pim Cuijpers, PhD



In the past 15 years a considerable number of studies have found evidence that it may be possible to prevent the onset of some mental disorders. Most evidence is available for depressive disorders, but a growing number of studies have focused on anxiety disorders and psychotic disorders. This paper reviews the studies which have examined the effects of preventive interventions on the incidence of mental disorders in people who do not meet criteria for a mental disorder at baseline. More than 20 studies have examined prevention of depressive disorders, and they have found an overall reduction in the incidence of about 25% compared with control groups. The problem of identifying the most optimal target groups for preventive interventions is also illustrated. This is a problem because most risk indicators have a low specificity, and most people with a risk indicator do not develop a mental disorder. Finally, this paper will show how other statistics, such as the exposure rate, the attributable fraction, and the number needed to treat can help in identifying the most optimal target groups for preventive interventions.

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Dialogues Clin Neurosci. 2009;11:447-454.

Keywords: depression; major depressive disorder; prevention; psychological intervention; review

It has long been thought that it is not possible to prevent the onset of mental disorders, because the processes involved in the etiology are too complex and not yet sufficiently understood. In the past 15 years, however, the knowledge about identifying target groups for prevention and about the effects of preventive interventions has increased considerably. A growing number of randomized controlled trials has shown that it is possible in some cases to actually prevent or at least delay the onset of mental disorders, including depressive disorders and anxiety disorders, and some studies indicate that it may even be possible to prevent the onset of psychotic disorders in high-risk groups (see review below). Research on effective prevention programs is very important for several reasons. First, effective prevention programs may potentially contribute to the reduction of the enormous burden of mental disorders.¹ Mental disorders account for 22% of the total burden of disease in established market economies, as measured in disability-adjusted life years lost,² with the common mental disorders (depression, anxiety, and substance use disorders) accounting for three quarters of the burden of all mental disorders. At any given moment, 150 million people suffer from a depressive disorder, 90 million suffer from a substance-related disorder, and each year a million people commit suicide. Mental disorders are associated with huge losses in quality of life in patients and their relatives, with increased mortality and morbidity, with high levels of service use, and with enormous economic costs.^{3,4}

Author affiliations: Department of Clinical Psychology and EMGO Institute, VU University Amsterdam, The Netherlands

Address for correspondence: Pim Cuijpers, PhD, Professor of Clinical Psychology, Department of Clinical Psychology, Chair, VU University and EMGO Institute, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands (e-mail: p.cuijpers@psy.vu.nl)

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Selected abbreviations and acronyms

AF	<i>attributable fraction</i>
ER	<i>exposure rate</i>
NNT	<i>number needed to treat</i>
OR	<i>odds ratio</i>

It is estimated that only half of the burden of the common mental disorders can be averted with existing treatment methods (both psychological and pharmacological) given maximized coverage (the number of people seeking treatment), clinician competence, and patient compliance with treatment.⁵ If we want to reduce the burden of mental disorders further, we can either develop new treatment methods that are considerably better than existing ones, or we can develop preventive interventions that result in reductions of new cases. The option for preventive interventions has not been examined very thoroughly, although it can be regarded as a promising way to reduce the burden of psychiatric diseases.⁵ Another reason why this research is so important is that it may increase our knowledge of the etiology of mental disorders. Until now, most mental disorders have been thought to be caused by multiple factors on different levels (physical, social, psychological), and it is not possible to predict which individual is going to develop the disorder and who is not. If it proves to be possible to prevent new cases of mental disorders, the interventions must somehow change the basic mechanisms that lead to the occurrence of the disorder.

This review will first define exactly what prevention is. Then, the research on the effects of interventions on the prevention of the incidence of new cases of mental disorders will be summarized. Finally, the possibilities of developing personalized preventive interventions, using new epidemiological methods to identify the most important high-risk groups for prevention, will be described.

What is prevention?

In the definition of depression which is currently used by most researchers and practitioners, depression comprises all interventions which are conducted before subjects meet the formal criteria for a mental disorder (according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, *DSM-IV*).⁶ Curative interventions are given to persons who suffer from acute disorders, and maintenance treatments are given to patients

with chronic disorders. In this spectrum of interventions, three types of prevention can be distinguished:

- Universal prevention is aimed at the general population or parts of the general population, regardless of whether they have a higher-than-average risk of developing a disorder. The best-known examples of universal prevention include school programs aimed at all students, whether they have an increased risk of developing a mental disorder or not, and mass-media campaigns, aimed at the general population.
- Selective prevention is aimed at high-risk groups, who have not yet developed a mental disorder. High-risk groups include people who have recently experienced a stressful life event or who experience a chronic stressor, such as divorce, losing a family member through death, caring for an ill family member, and unemployment.
- Indicated prevention is aimed at individuals who have some symptoms of a mental disorder but do not meet diagnostic criteria. Indicated prevention is aimed at people who already suffer from some (depressive) symptoms.

Is prevention of mental disorders effective?

In the past few decades, several hundred controlled studies have examined the effects of mental health programs aimed at preventing mental health problems at school,^{7,8} substance use and abuse at school,⁹ work-related stress,¹⁰ distress among caregivers for the elderly,^{11,12} child abuse,^{13–15} and many other conditions. This considerable body of research has shown that some prevention programs in mental health are capable of strengthening protective factors, such as social skills, problem-solving skills, stress-management skills, prosocial behavior, and social support; that these programs can reduce the consequences of risk factors, psychiatric symptoms, and substance use; and that they may have positive economic effects.

However, only a small proportion of these studies have focused on possibilities for actually preventing the onset of new cases of mental disorders.⁶ In recent years, a growing number of studies have examined whether prevention programs are actually capable of reducing the incidence of cases of mental disorders as defined by diagnostic criteria. In these studies a standardized diagnostic interview at baseline is used to exclude the pretest presence of a full-blown depressive disorder and to

examine the incidence of depressive disorders at follow-up (again with a diagnostic interview). In the following, we will review these studies.

Prevention of depressive disorders

Most research has focused on the prevention of depressive disorders. Following the first studies conducted in the 1990s,¹⁶⁻¹⁸ the number of studies has increased rapidly since 2000. We recently conducted a meta-analysis of these studies,¹⁹ and found a total of nineteen studies in which subjects with a depressive disorder according to DSM criteria at baseline were excluded, and only subjects with no formal depressive disorder were included. All these studies examined whether the incidence rate of mental disorders was reduced in the recipients of preventive interventions compared with subjects who did not participate in such an intervention. We found that the overall incidence rate ratio was 0.78 (95% CI: 0.65~0.93). The incidence rate ratio is the incidence rate of developing a depressive disorder in experimental subjects relative to the incidence rate in control subjects. An incidence rate ratio of 0.78 indicates a reduction of the risk of developing a depressive disorder in the next year of about 22% compared with people in the control groups. This study indicates that prevention of new cases of depressive disorders is indeed possible, and could be a realistic strategy to reduce the enormous burden of these disorders, next to treatment of existing depressive disorders. Preventive interventions have been developed in several settings, including the school setting, prevention of postpartum depression in pregnant women, and prevention of depression in general medical disorders.

A considerable number of studies has examined the possibilities of prevention in the school setting.^{20,21} However, most of these have only examined whether school programs are capable of reducing the overall level of depressive symptoms in students. Although this is interesting in its own right, and positive effects may be indicative of effects on depressive disorders, the results of these studies do not result in clear evidence of a preventive effect of these interventions on depressive disorders. Until now, only four studies have examined preventive interventions aimed at the reduction of the incidence of depressive disorders at school.^{17,22-24} Two studies used a universal intervention aimed at all students, regardless of whether they had an increased risk

of developing a depressive disorder.^{25,26} In both studies, no significant effect on the onset of depressive disorders was found. In three studies, the effects of an indicated intervention were used examined,^{17,22,24} and these had mixed results, with one study finding strong and significant effects on the incidence of new depressive disorders at 1-year follow-up.¹⁷ Most interventions in the school setting, both universal and indicated, have used cognitive behavioral group interventions.

There is also a considerable number of studies that have examined the possibilities of preventing postpartum depression (PPD),^{27,28} but again most of these studies did not use diagnostic criteria at pretest and post-test, to exclude women who already had a depressive disorder at pretest, and to examine the effects of prevention on the incidence. Most studies have used self-report measures, and have only examined whether the level of depressive symptoms have decreased in the prevention groups compared with control groups. Many of these studies used cognitive behavioral interventions,²⁹⁻³⁰ although other studies used psychoeducational interventions,³¹ debriefing,³² and interpersonal psychotherapy.^{33,34} A recent meta-analysis of studies on prevention of PPD did not find clear evidence that preventive interventions during pregnancy may reduce the incidence of postpartum depression.²⁷ This meta-analysis did not, however, focus on studies in which women who met diagnostic criteria for a depressive disorder were excluded at pretest, and in which the incidence of depression in treatment and control groups were established according to diagnostic criteria. In the earlier described meta-analysis, seven randomized controlled in which diagnostic instruments were used, could be included. These resulted in an incidence rate ratio of 0.65 (95% CI: 0.41~1.05; $P < 0.1$).

Another group of studies has focused on the prevention of depression in general medical disorders. Several groups of general medical patients have been examined in prevention studies, including adolescents with newly diagnosed epilepsy and subthreshold depression (but no major depressive disorder),³⁵ older patients with neovascular macular degeneration,³⁶ and stroke patients.³⁷ Three studies have examined the possibility of preventing depressive disorders in primary care.^{16,38,39} Most studies in this field used cognitive behavior therapy^{16,35,38} or problem-solving therapy as intervention.^{36,37}

One of the studies in primary care used a stepped-care intervention. Such stepped-care interventions are inter-

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esting because they seem to have larger effects than single interventions (with a reduction of the incidence of 50%),³⁹ and because they devote most intervention time to those who need it most. In such a stepped-care approach, the first step is watchful waiting. This means that no specific intervention is conducted for 6 to 8 weeks, because many subclinical depressive symptoms recover spontaneously without intervention. In the second step, a guided self-help intervention is provided to patients. Guided self-help has been proven to be effective in the reduction of depressive symptoms,⁴⁰ and may be sufficient for some patients. If the guided self-help is not sufficient and patients continue to have depressive symptoms, a brief psychological intervention is provided, such as problem-solving therapy, or a brief cognitive-behavioral intervention. When this is not enough, patients are referred to specialized mental health care where they receive intensive treatment with antidepressant medication.

Prevention of other mental disorders

Although most research has examined the effect of prevention on the incidence of depressive disorders, a growing number of studies has examined the possibilities of preventing the onset of anxiety disorders and psychotic disorders in high-risk populations.

A considerable number of studies has examined the possibility of preventing the onset of post-traumatic stress disorder (PTSD) with debriefing interventions.⁴¹ Unfortunately, many of these studies did not use diagnostic instruments to establish the presence of PTSD at follow-up. However, the studies that have been conducted seem to indicate that debriefing increases the risk of developing PTSD, instead of decreasing this risk.^{41,42} Several other studies have examined the possibilities of prevention of other anxiety disorders. In an early study among patients with panic attacks who visited the emergency room of a hospital, it was found that exposure therapy had better outcomes than reassuring them that there was no physical illness.⁴³ In a more recent study among persons with high levels of anxiety sensitivity, it was found that preventive training consisting of psychoeducation and behavioral exercises significantly reduced the risk of developing an anxiety disorder in the following 2 years.⁴⁴ In another study, it was found that the incidence of panic disorder in people with sub-threshold panic attacks is lower at 6 months' follow-up

in those who attended a 1-day preventive workshop compared with those on a waiting list.⁴⁵

In recent years, several studies have examined the effects of preventive interventions on the onset of psychotic disorders.⁴⁶⁻⁴⁹ In these studies, patients with subthreshold symptoms of psychotic disorders (without meeting full diagnostic criteria) are randomized to cognitive behavior therapy or a control condition. These studies show significant reductions of transition to psychotic episodes in those who have received the preventive interventions, compared with those in the control groups, although the longer-term effects are not so clear.^{47,48}

Problems in identifying target groups for preventive interventions

In the preceding paragraphs it was shown that a considerable number of recent studies have examined the effects of preventive interventions on the incidence of mental disorders, and, when taken together, with considerable success. However, the success of these interventions depends very much on the selection of the right target populations. The first step in every intervention is to select a target population which has an increased risk of developing a mental disorder within the coming months or year. In the following paragraphs, we will explain why this selection of high-risk groups is very complicated, and present some recently developed methods in epidemiology to solve the problems in the selection of target groups.

In the past few decades, an enormous body of research has shown that many biological, psychological, and psychosocial risk indicators are associated with the onset of mental disorders. These include genetic factors, characteristics of personality, social economic status, stress and burden, urbanization, loneliness, life events, and somatic factors, such as complications during pregnancy, developmental disorders, neuroendocrinological factors, and general medical disorders. Note that we define these variables as risk indicators, and not as risk factors, as risk factors suggest that these are causally associated with the onset of depressive disorders. Risk indicators only indicate that there is an association between the variable and the onset, while no causal association is assumed. In principle, these risk indicators can be used to identify target groups for preventive interventions. In the next part of this paper, we will show that several groups of interventions actually have focused on such high-risk groups.

Although many risk indicators are known to be associated with the onset of mental disorders, most of them have a low specificity. This low specificity implies that most subjects who are exposed to the risk factor do not develop the disorder, and that one such risk factor by itself is not sufficient to bring the disorder into being.^{50,51} Furthermore, most risk indicators are related to lifetime risk, while target populations for preventive interventions must have an increased risk at the shorter term. Suppose, for example, that the risk of developing a major depressive disorder in the general population is 2.5% in 1 year.^{52,53} If a high-risk group has a relative risk of developing a depressive disorder of 4.00, this will be highly significant (if the research population is large enough). However, this means that still only about 10% of the high-risk group will actually develop a depressive disorder, and about 90% will not.

Many epidemiological researchers are satisfied after finding a highly significant relative risk of 4.00, but from the point of view of prevention this is clearly not enough. A high-risk group will probably be difficult to motivate for participation in a preventive program if only 10% eventually will develop the disorder, apart from the question of whether it is ethically acceptable to identify such a population as being “at risk” when most are in fact not at risk, or to intervene in such a population when for the vast majority of participants the intervention is not needed, and thus the time they spend on it is, in a sense, wasted. Furthermore, such an intervention is probably not very efficient or cost-effective, because the majority will never develop a disorder and the intervention has no preventive effect in this majority.

From the perspective of preventive intervention research, this low specificity is also problematic because very large numbers of subjects are needed to provide sufficient statistical power for these intervention studies.⁵¹ Suppose, for example, that we would be able to motivate people from the high-risk group (10% of whom will develop a mental disorder in the following year) to participate in a preventive intervention. In order to show that such an intervention is capable of reducing the incidence from 10% to 5% (a risk reduction of 50%), we would need about 950 persons in a controlled trial (assuming a statistical power of 0.80; alpha level 0.05; calculations in STATA/SE 8.2). Trials of this size are logistically complex, expensive, and have a high risk of failure.

Towards an improved method of identifying target groups for prevention

As previously stated, traditional indicators of the strength between a risk indicator and the incidence of a mental disorder are not sufficient when we want to identify the best target populations for preventive interventions and to develop personalized interventions. Improvements can be made by selecting target groups while using indices other than odds ratios (ORs), relative risks (RRs) or incidence rate ratios (IRRs) alone, and in particular by studying the cumulative effect of joint exposures to several risk indicators rather than the effect of a single risk indicator. The proposed method can be carried out in several steps.

First, a set of significant risk indicators is identified such that each of them has a statistically significant impact on the likelihood that the disorder will develop. To do this any of the available measures of association for binary outcomes (OR, RR or IRR) can be used.

Second, if an OR can be calculated, then it is also possible to say how many people are exposed to that risk indicator. Call this measure “exposure rate” (ER). For prevention the ER is important, because it tells us how many people have to be targeted by the preventive intervention. Clearly, smaller groups (smaller ER) are associated with less effort and hence lower costs of delivering the intervention.

Third, with the OR and ER in hand one can calculate the population attributable fraction (AF). The AF indicates by how many percent points the current incidence rate of the mental disorder in the population could be reduced when the adverse effect of the risk indicator is completely blocked.⁵⁴⁻⁵⁶ This equals the maximum possible health gain of a completely successful preventive intervention.

Fourth, if the OR can be calculated, then it is also possible to obtain the risk difference (eg, under a linear probability model) and its inverse: the number needed to treat (NNT). In the context of these analyses the NNT can be interpreted as the number of people who should be the recipients of a preventive intervention to avoid the onset of the disorder in one person. Again we have to assume that the preventive intervention is completely successful in containing the adverse effect of the risk factor. This assumption is not realistic, but the NNT may still help to create a hierarchy of risk indicators to be targeted in prevention.

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Now comes the most important part of the method. We want to maximize the health gain (large AF) and minimize the effort to generate this health gain by targeting the smallest possible group (small ER) in the most efficient way (small NNT). Best values overall can be found by looking at combinations of risk indicators. That is, we can see what combinations of exposures (joint exposures) help to minimize and maximize the indices, such that a target group is selected where prevention is most likely to become cost-effective.

There are several ways of finding specific combinations of risk indicators, whether genetic or environmental, that meet the above criteria, including sophisticated statistical techniques, such as classification and regression trees (CART) analysis, and bootstrap aggregation (bagging).^{57,58} The most straightforward method, which we use here for illustrative purposes, is to select significant predictors of incidence (with standard techniques such as logistic regression) after which all possible combinations of these significant risk indicators are explored in terms of maximizing the OR and AF, and minimizing ER and NNT associated with each of the joint exposures. We used this approach in a population-based sample of older adults,⁵⁴ and found that subjects with (subclinical) depressive symptoms, functional limitations, a small social network, and female gender comprised only 8% of the total population (ER) while 24.2% of the new incident cases could be attributed to this group (AF). The number of subjects from this population that would have to receive a preventive intervention in order to prevent one incident case (NNT) was 4 (assuming that the intervention is 100% successful).

There is little doubt that these methods will help to identify the best target groups for preventive interventions in the near future and to develop personalized interventions. However, at this moment these methods have not yet been applied in intervention studies.

Conclusion

This paper is intended to illustrate why prevention of mental disorders is important. Reasons for its importance include its very high prevalence, incidence, disease burden, and its huge economic costs of depression. It is also important because current treatments can reduce the disease burden only to a limited extent, even when only evidence-based treatments are given and all patients receive such an intervention.

In the past 15 years a growing number of studies has shown that interventions to prevent the onset of depressive disorders are probably effective, and can reduce the incidence by about one quarter. Prevention of anxiety disorders and psychotic disorders may also be effective, although the number of studies in these areas are lower. It is not clear whether these preventive interventions have actually prevented the onset of mental disorders altogether, or only delayed the onset. In both cases, however, the health benefits of preventive interventions are considerable.

In the next few years, the internet will probably provide new opportunities for the broad implementation of preventive interventions, because access is easy, cheap, and effective. Another important development is stepped-care interventions, which are interesting because they may have stronger effects than individual interventions and spend most resources on those who need it most.

It has also been shown that traditional epidemiological research can not identify the best target populations for prevention. Relatively simple statistics, such as the exposure rate, the population attributable fraction, and the number needed to treat can be used to select those high-risk groups which are as small as possible, but explain as many of the new incident cases as possible. These methods will probably help in the further development of personalized preventive interventions. □

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La prevención: un objetivo alcanzable en la medicina personalizada

En los últimos quince años numerosos estudios han encontrado evidencias de que puede ser posible prevenir la aparición de algunos trastornos mentales. Si bien la mayor evidencia de que se dispone corresponde a los trastornos depresivos, existe un número creciente de estudios focalizados en los trastornos de ansiedad y psicóticos. Este artículo revisa los estudios que han examinado los efectos de las intervenciones preventivas en la incidencia de los trastornos mentales en personas que no cumplen con los criterios de un trastorno mental en el estado basal. Más de veinte estudios han examinado la prevención de los trastornos depresivos, y han encontrado una reducción global de la incidencia de alrededor del 25% comparado con los grupos control. También se ilustra el problema de la identificación de los grupos blanco más específicos para realizar intervenciones preventivas. Esto es un problema porque la mayoría de los indicadores de riesgo tienen una baja especificidad, y la mayor parte de las personas con un indicador de riesgo no desarrolla un trastorno mental. Por último, este artículo muestra cómo otras variables (frecuencia de exposición, fracción atribuible y número necesario para tratar) pueden ayudar a identificar los grupos blanco más específicos para las intervenciones preventivas.

La prévention : un objectif accessible pour la médecine personnalisée

Un nombre important d'études a montré au cours de ces 15 dernières années qu'il pourrait être possible de prévenir la survenue de certains troubles mentaux. La plupart des résultats concernait les troubles dépressifs mais de plus en plus d'études se sont intéressées aux troubles anxieux et psychotiques. Cet article passe en revue les études qui ont examiné les effets des actions de prévention sur l'incidence des troubles mentaux chez des sujets qui ne présentaient pas initialement les critères de pathologies psychiatriques. Dans plus de 20 études analysant la prévention des troubles dépressifs, l'incidence a globalement diminué d'environ 25 % comparée aux groupes témoins. Il est difficile d'identifier les meilleurs groupes cibles pour les actions préventives car la plupart des indicateurs de risque ont une faible spécificité et la plupart des personnes ayant un indicateur de risque ne développent pas de maladie mentale. Enfin, cet article se propose de montrer comment d'autres variables statistiques, comme le taux d'exposition, la fraction attribuable et le nombre de sujets ayant besoin d'être traités peuvent aider à identifier les cibles les plus adaptées des interventions de prévention..

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Shared decision making in mental health: prospects for personalized medicine

Robert E. Drake, PhD; Delia Cimpean, MD; William C. Torrey, MD



This paper describes the shared decision-making model, reviews its current status in the mental health field, and discusses its potential impact on personalized medicine. Shared decision making denotes a structured process that encourages full participation by patient and provider. Current research shows that shared decision making can improve the participation of mental health patients and the quality of decisions in terms of knowledge and values. The impact of shared decision making on adherence, illness self-management, and health outcomes remains to be studied. Implementing shared decision making broadly will require re-engineering the flow of clinical care in routine practice settings and much greater use of information technology. Similar changes will be needed to combine genomic and other biological data with patients' values and preferences and with clinicians' expertise. The future of personalized medicine is clearly linked with our ability to create the infrastructure and cultural receptivity to these changes.

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Dialogues Clin Neurosci. 2009;11:455-463.

Keywords: *shared decision making, patient choice, informed decision making*

The current complexity of treatments and outcomes in modern medicine presents a fundamental dilemma. Few medical treatment decisions involve a clear best choice; the typical medical decision involves trade-offs among multiple partially effective interventions with different risks. Consider the case of surgical interventions. Placing a pin in a fractured hip represents a rare case of a consensual best treatment for almost every patient. In many other common surgical situations, the evidence is considerably more complicated. For example, surgery for benign prostatic hypertrophy produces better urine flow at the risk of incontinence and impotence. When men understand the tradeoffs accurately, many prefer medications or watchful waiting.¹ Similarly, for early breast cancer, spinal disk injury, prostate cancer, rotator cuff injuries, uterine fibroids, coronary artery disease, and many other surgical conditions, choice among different interventions with complex outcomes and adverse effects is the rule.² This fundamental dilemma gives rise to the belief that patients should be involved in making medical decisions generally, and to the paradigm of shared decision making more specifically.

Shared decision making assumes that two experts (or teams of experts) should collaborate in making complex medical decisions.³ The health care provider (often a team of professionals) brings expertise in understanding the medical problem, the possible interventions, and the potential benefits and risks of alternatives. The patient

Author affiliations: Dartmouth Psychiatric Research Center, Lebanon, New Hampshire, USA

Address for correspondence: Dr Robert E. Drake, Psychiatric Research Center, 2 Whipple Place, Suite 202, Lebanon, NH 03766, USA (e-mail: robert.e.drake@dartmouth.edu)

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(often assisted by family or support network members) brings expertise related to understanding the individual's values, goals, supports, and preferences. Shared decision making generally involves both partners presenting their respective views and then negotiating a plan that both agree is ethical, consistent with the evidence, congruent with the patient's preferences, and practical. Conceptually, shared decision making falls between two extreme approaches to medical decision making: the paternalistic and the autonomous decision models.⁴ In the traditional, paternalistic model, the physician assesses what is best for a particular patient, based on scientific evidence and clinical judgment, and makes the decision. In the autonomous decision model, the patient is presented with information, weighs the information, and makes the choice unilaterally.

As a simple example of shared decision making, consider a young woman who suddenly develops radiating pain as a result of a back injury. Her medical exam and magnetic resonance imaging reveal a lumbar disk protrusion. Her physician describes alternative approaches that include surgery, nerve blocks, a back brace, physical therapy, and watchful waiting. The patient and her parents are averse to surgery, especially when they understand the risks, and prefer conservative treatment. The physician agrees that wearing a brace and waiting for 2 months to re-evaluate the injury is reasonable. Two months later, she is much improved, and they agree that exercise is the best strategy.

Now consider a more complex decision. A second young woman develops a breast lump and is diagnosed with uncomplicated early breast cancer. Her physician reviews with her the surgical alternatives (lumpectomy vs breast removal) as well as adjunctive chemotherapy and radiation therapy, and describes the risks and benefits of each. Due to the early stage of illness, the physician clearly believes that the patient is an excellent candidate for lumpectomy. Because of a strong family history and the experience of watching her mother die of breast cancer, however, the young woman prefers bilateral mastectomy. After further discussion with the patient and her husband, the physician understands and accepts the patient's decision and performs the more radical surgery. In this case, the physician initially disagrees with the patient's choice but accepts the patient's preference and right to make the decision.

The medical literature and research evidence on shared decision making, decision supports, and decision aids are

extensive and growing rapidly.⁵ For example, there are now literally hundreds of decision aids to help patients make medical decisions. The diversity of these instruments has led recently to the development of international standards.⁶ The evidence shows that decision aids help patients to make more informed decisions that are more congruent with their values and preferences.⁷ Longer-term effects on basic health outcomes are not yet well studied.

Shared decision making in mental health: current status

Several arguments suggest the importance of shared decision making in mental health. First and foremost, effective mental health care should be person-centered.^{8,9}

As is true with other long-term illnesses,^{10,11} empowering people to be knowledgeable and active in managing their own mental illnesses is critical.¹² Decisions related to chronic illnesses differ from acute-care decisions in several ways: for example, there are many opportunities to make and revisit the decisions, and the patient must take much greater responsibility in carrying out decisions daily.¹⁰ Because of personal values and subjective responses, patients themselves can best evaluate trade-offs in efficacy and side effects.^{13,14} In mental health, shared decision making enhances the working relationship needed to optimize long-term outcomes.¹⁵ For example, learning to manage one's illness with medications involves a dynamic, longitudinal process that encompasses resolving decisional conflicts, conducting experiments, balancing positive and negative effects, and making changes. A close working alliance between practitioner and client is the *sine qua non* of success.

In addition to these practical concerns, others have made ethical and legal arguments for shared decision making. Autonomy—the right to make decisions regarding one's body—has long been a fundamental principle of Western medical ethics.¹⁶ Recognizing the importance of autonomy, the legal standard for medical care is shifting from informed consent to informed choice among reasonable alternatives.¹⁷

Most mental health patients express a desire to participate in making decisions regarding medications and hospitalizations.¹⁸⁻²¹ Nevertheless, shared decision making is not prominent in widely disseminated psychiatric medication algorithms²² and not usually practiced in daily medication management.¹⁵ Patients with severe and per-

sistent mental illnesses report that their perceived role in making medical decisions is usually passive.^{18,21,23} Further, many psychiatrists consistently report that shared decision making is not applicable to decisions regarding medications and hospitalizations due to patients' decisional incapacity.^{24,25}

At the same time, the evidence in support of shared decision making in mental health is expanding rapidly. First, nearly all psychiatric patients, even the great majority of those with the most severe disorders such as schizophrenia, are capable of understanding treatment choices and making rational decisions.²⁶⁻²⁸ Like many other patients with limited education, learning disorders, or other disadvantages, some require repetition of information or multimodal sources of information.²⁹ Also, some psychiatric patients experience temporary decisional incapacity, such as during psychotic episodes, and may elect to establish psychiatric advanced directives to cover such periods of decisional incapacity.³⁰

Second, shared decision making constitutes a core principle of many effective mental health practices and may, in part, explain their effectiveness.^{12,31-33} For example, honoring the client's preference for type of job is a fundamental principle of supported employment, and the entire model follows the client's decisions about when to search for a job, how many hours to work, whether or not to disclose illness to the potential employer, supports on the job, manner of follow-up, and so on.³⁴ Emphasis on shared decision making is also built into illness management and recovery,¹² behavioral family therapy,³⁵ integrated dual disorders treatment,³⁶ and systematic medication management.³⁷ Assertive community treatment, which was historically criticized for paternalism, is also becoming more client-centered.³⁸

Third, although research on shared decision making in mental health is in its infancy, seven initial randomized controlled trials support its effectiveness. Malm et al³⁹ provided multiple shared decision-making sessions within a treatment program for schizophrenia patients, and found that the experimental group had higher ratings of patient satisfaction than controls at 2 years. Van Korff et al⁴⁰ provided multiple sessions of shared decision making to depressed patients, and found better adherence and depression symptom outcomes favoring experimental over control participants at 3, 6, 9, and 12 months. Van Os et al gave one session of shared decision making to patients with schizophrenia and their doctors in a randomized clinical trial and found that the experimental

patients reported improvements in quality of patient-doctor communication and that the intervention induced changes in medication management immediately.⁴¹ Hamann et al⁴² conducted a randomized controlled trial with schizophrenia inpatients and found increased knowledge and perceived involvement in decisions by the experimental group during hospitalization. Priebe et al⁴³ used a cluster randomized design to study use of a computer-mediated intervention to structure patient-clinician interactions regarding quality of life and needs for care every 2 months for a year. Schizophrenia patients in the experimental group had better subjective quality of life, fewer unmet needs, and greater satisfaction with treatment at 1 year. Loh et al⁴⁴ used a cluster randomized design to study a shared decision-making intervention with depressed patients. At 6- to 8-week follow-up, experimental group patients reported greater participation in decision making and greater satisfaction with care, although the intervention did not impact severity of depressive symptoms. Joosten et al⁴⁵ used a cluster randomized design to study shared decision making within inpatient addiction treatment programs. Patients who received shared decision making rather than traditional decision making had greater reductions in drug use and psychiatric symptoms at 3-month follow-up. Woltmann⁴⁶ used a cluster randomized design to study shared decision making during one session of treatment planning between case managers and clients with severe and persistent mental illnesses. Clients and case managers in the shared decision-making group were more likely to report that decisions were collaborative.

Thus, as in general medicine, the initial research in mental health shows that shared decision making increases the quality of decisions (knowledge, participation, and congruence with values), but there is minimal evidence regarding objective health outcomes. Long-term studies of health outcomes related to greater knowledge, participation in illness self-management, and better relationships with practitioners need to be evaluated.

The doctor's role in shared decision making

In this section, we illustrate some of the barriers to implementing shared decision making in mental health by examining the outpatient psychiatrist's role. The central point is that practising shared decision making involves much more than endorsing the concept. The complex structure and process of care must support the desired

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practice. To achieve shared decisions, psychiatrists and patients need significant time,⁴ facilitated communication,⁴⁷ and easy access to clinically useful current scientific knowledge.⁴⁸ These conditions do not currently exist in psychiatric office practice in the US. Therefore, the process of care will need to be redesigned to make shared decision making the easy and natural way to practice.⁴⁹

Psychiatric office visits are complex and dynamic interactions that are packed with psychological, interpersonal, and practical tasks. These include establishing a trusting relationship; identifying goals for the encounter; gathering needed information, such as assessing and addressing symptoms, function, and/or side effects of treatment; planning the next steps; documenting the encounter; prescribing medications; communicating with other providers; and filling out forms.⁵⁰ The time for shared decision making must come from time usually spent on these other tasks because expanding visit length is currently prohibited by costs.

Addressing the time dilemma will require re-engineering office practice and using information technology.⁵¹ At the microsystem level, a trained and organized team (an activated patient, support from other staff, and a well-designed information system) can create efficiencies in the flow of the office visit.⁵² Team members other than the psychiatrist can elicit and record the patients' current concerns, experiences, and values.⁵³ They can also obtain required vital signs, track down lab values, fill out sections of forms the psychiatrist needs to sign, prepare prescriptions for physician review and signature, and help the patient to be as active as possible, including direct participation in collecting information through patient portals to the electronic medical record. A well-designed electronic medical record can increase efficiency (and improve care) by collecting and graphically displaying patient-entered information, laying out evidenced-based treatment algorithms, and streamlining common required tasks such as clinical documentation, prescription writing, and clinical communication to other health care providers.⁵⁴

Many people, including both those with and without psychiatric symptoms, find it difficult to express themselves in doctors' offices. The medical care process is not transparent, and people do not naturally know what information is relevant and important to communicate. Further, medical settings are often intimidating, and people are nervous. Nevertheless, the voice of the patient must be at the heart of the decision-making process. Without hearing the patient's chief current concerns, subjective life

experiences, and core values, decisions lack both data and salience to the patient's life.⁵⁵

Currently, all information about the patient's perspective comes from the dialog between the psychiatrist and the patient during the busy office visit. Important issues, such as whether the patient's chief concerns for the session are routinely elicited and whether the patient experience is gathered in a valid, reliable manner, are up to self-designed practice habits of the psychiatrist.⁵⁵ Without a system designed to elicit, organize, and amplify the voice of the patient, the psychiatrist can easily miss information that would make the clinical decisions much more informed, relevant, and collaborative.

Re-engineering the office could facilitate communication in three ways. First, the redesign could increase the confidence and ability of patients to be active participants in the care process by explicitly welcoming them when they arrive for service, orienting them to the care process, and providing accessible education on the illnesses and the treatment options. Second, the patient's voice could be amplified by explicitly eliciting and documenting chief concerns, experiences, and core values. If this inquiry occurs before the actual encounter, the information is more likely to be complete, the patient's questions will be written down so they are not forgotten, and the visit time is freed up for double-checking understanding and for in-depth discussion. Finally, symptoms, medication side effects, and functional status questions can be asked in a systematic fashion using standardized instruments by computer,^{55,57,58} and the longitudinal results can be displayed graphically. Computerization allows the patient and the psychiatrist to examine progress and base discussions on longitudinal standardized data as a team, practising individualized evidence-based medicine.

The essence of evidence-based practice is to use knowledge gained through research to inform specific clinical choices. Decision supports are more likely to be used if information is available in the regular flow of the office visit. Connecting the patient and the psychiatrist with the evidence at the time that it is needed and in a form that both can understand is therefore another critical element of redesigning the office visit to facilitate shared decision making.⁴⁹

Both patients and psychiatrists need timely access to research findings. Patients can benefit from orienting information about the illnesses and what is known about options to minimize symptoms and maximize function. Psychiatrists and patients together can benefit from

research-supported charts and algorithms that condense whole fields of knowledge into research-supported paths for care.^{59,60} Psychiatrists also need direct access to detailed information when it is too voluminous or complex to remember. Currently, this includes decision support in the form of drug-drug interactions that appear as safety warnings in electronic records. Soon, it will encompass individualized medicine: historical, medical, physiological, and genetic information that will summarize patient-specific risk factors.

The needs of people with severe and persistent mental illnesses do not vary radically from site to site. Therefore, a transformational psychiatrist office visit process that weaves together all the elements that are needed for efficient evidence-based psychiatric practice could be designed, tested, packaged, and implemented widely. Doing so shifts the office visit process to one that is specifically designed to meet the needs of people who have an ongoing psychiatric illness or vulnerability using principles that have been shown to be helpful in improving the care of people with other persistent health difficulties.⁶¹

Personalized mental health care and shared decision making

Creating a flow of care that makes sharing decisions natural and efficient will be even more important when we have access to tests that will provide us with person-level information that is relevant to mental health care decisions. The current state of treatment selection in mental health is characterized by multiple choices, with little evidence to guide decisions to select initial or subsequent treatments.^{62,63} Genetic or molecular factors might help inform treatment selection by identifying a priori people likely to have side effects, such as treatment-emergent suicidal ideation in response to antidepressants,⁶⁴ or metabolic syndromes with antipsychotic treatment.⁶⁵ Genetic testing might also identify people needing particularly low or high doses of medications,⁶⁶ people more likely to attain remissions,^{67,68} or even people more likely to respond to a certain medication mechanism of action.⁶⁹ Identification of individual genetic or molecular factors, in the future, may help establish diagnoses in people with subsyndromal symptoms or unclear diagnoses, as well as further inform asymptomatic relatives of people with mental illnesses in making reproductive decisions and personal lifestyle choices.⁷⁰

At the same time, information of this type might also create social and psychological risks and pessimism in regard to the effectiveness of treatments.⁷¹ Potential adverse consequences could affect emotional well-being, family relationships, employment, and insurance.^{72,73} Thus, the potential of psychiatric genomics has fueled ongoing ethical and legal debates.^{74,75}

The availability of such complex information needs to be paired with a structured system of communicating the benefits and the risks of testing to patients to allow its effective incorporation into the process of shared medical decision making. In other areas of medicine, studies of communication of genetic information to patients have identified the importance of education, risk communication, and emotional support.⁷⁶⁻⁷⁸

Genetic information dramatically increases the complexity of risk. In cancer genetics, Huiart et al⁷⁹ outlined the difference between the individual risk of inheriting or transmitting predisposing genes and the individual risk of developing the disease. This is highly relevant for mental health, as most neuropsychiatric disorders are polygenic, and any single gene variation may have minimal impact on individual risk. Gene variations can have additive effects on the expression of a phenotype,⁸⁰ or a certain gene variation might be expressed only through interaction with the environment.⁸¹ The ability of a test to identify gene variation might be different from its ability to identify the phenotype of interest. Furthermore, for example in cytochrome system testing, identifying a certain phenotype, such as slow metabolizers, may or may not have clinical utility, depending on other factors, such as ethnicity or the medication choice involved.⁶⁶

As in other areas of medicine, communicating the meanings of uncertainty, risk, and statistics in mental health conditions is difficult.⁸² Patient education needs to include not only information about choices but also information to enhance statistical literacy. Several research findings have helped this field. For example, using absolute risks rather than relative risks and transforming probabilities into natural frequencies displayed as pictograms facilitate communication and understanding.^{83,84}

Specialized genetic counselors have traditionally provided risk information in medical genetics. More recently, decision aids focused on risk communication and patient education have become prominent.^{77,85} A recent review of risk communication interventions found that decision aids improved knowledge, but did not nec-

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essarily decrease anxiety.⁷⁷ Availability of decision aids prior to the encounter with a clinician did, however, increase time for discussion of personal risk rather than education.⁸⁶

Individual counseling has been identified as an important element of genetic communication to improve risk perception and to address the psychological and social effects of genetic testing on the patient and the family.^{71,77,87,88} Inaccurate perceptions of risk after communication were associated with the psychological health of the individual.⁷⁹ One-on-one counseling was associated with reduced decision conflict in general medicine,⁸⁹ but research on counseling related to genetic risk in mental health has not yet been done. Joint psychiatrist-genetic counselor consultation and family-based approaches have been proposed in mental health.⁹⁰

Psychiatrists, as well as other medical providers, score low on scales of patient involvement in decision making,⁹¹ perhaps in part because traditional genetic counseling has been based on autonomous choice models.⁹² Increased patient activation was described when mental health patients' own strategies for well-being and recovery were identified and supported.¹⁵ In general, patients expect and prefer help with decision making in studies of genetic information communication.^{78,93}

Shared decision making in mental health will need to incorporate, in the future, effective communication regarding genetic and molecular testing. Structured assessments prior to the consultation will facilitate expression of the patient's goals and values, including goals for genetic testing. Decision aids provided prior to the consultation could increase patients' knowledge and individualize information. The encounter with a provider should facilitate risk communication and decision making.

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Limitations

The barriers to shared decision making are legion.⁹⁴ Clinicians lack familiarity and training, sometimes disagree with the concept, and often have concerns regarding decisional capacity and legal responsibility. Patients often lack the information, empowerment, motivation, and self-efficacy needed to participate in shared decision making. Mental health systems almost universally lack the needed computer infrastructure. At a basic science level, concerns involve communicating uncertainty and risk, biases in many decision aids, and human biases in decision making in general.^{95,96} For example, mental health patients, like others, are biased by optimism regarding their own health, are confused by too many choices, have difficulties understanding statistical risks, and are influenced by biased information from industry. These issues need to be clarified by further research and addressed at many levels: basic decision-making science, clinician training, structural implementation, electronic infrastructure, patient empowerment, and so forth.

Summary and conclusions

Implementing shared decision making in routine mental health care offers considerable promise in terms of ethics, quality, informed decisions, patient satisfaction, enhanced ability for self-management, improved adherence, and meaningful outcomes. Putting these potentialities into everyday practice will be fraught with difficulties. Now is the time to address these barriers through research on shared decision making, as the information explosion and personalized medicine will require new educational structures, communication patterns, and decision-making forms. □

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La toma de decisiones compartidas en salud mental: perspectivas para la medicina personalizada

Este artículo describe el modelo de la toma de decisiones compartidas, revisa su situación actual en el campo de la salud mental y discute su potencial impacto en la medicina personalizada. La toma de decisiones compartidas traduce un proceso estructurado que fomenta la participación total del paciente y del proveedor. La investigación actual muestra que la toma de decisiones compartidas puede mejorar la participación de los pacientes mentales y la calidad de las decisiones en términos del conocimiento y los valores. Se debe estudiar el impacto de la toma de decisiones compartidas en la adherencia, el auto manejo de la enfermedad y las consecuencias en la salud. La implementación de la toma de decisiones compartidas en líneas generales requerirá de una reingeniería del circuito de la atención clínica en los ambientes de práctica cotidiana y un mayor empleo de la tecnología de la información. Se necesitarán cambios similares para combinar datos genómicos y otros datos biológicos con los valores y preferencias de los pacientes, y con la experiencia de los clínicos. El futuro de la medicina personalizada está claramente relacionado con nuestra capacidad de crear la infraestructura y la receptividad cultural a estos cambios.

Prise de décision partagée en santé mentale : en quête d'une médecine personnalisée

Cet article décrit le modèle de prise de décision partagée, le resitue dans le cadre actuel de la santé mentale et analyse son influence potentielle dans la médecine personnalisée. La prise de décision partagée est un processus structuré qui encourage la participation entière du patient et du médecin. La recherche actuelle montre que cette prise de décision peut favoriser la participation des patients psychiatriques et la qualité des décisions en termes de connaissances et de valeurs. Il faut en étudier l'influence sur l'adhésion au traitement, la prise en charge individuelle de la maladie par le patient et l'évolution de son état de santé. La mise en œuvre étendue de cette prise de décision partagée nécessitera de réorganiser les soins cliniques dans le cadre d'une pratique de routine et d'utiliser de manière plus importante les technologies de l'information. Associer la génomique et les autres données biologiques avec les préférences des patients et l'expérience des médecins demandera également des changements. L'avenir de la médecine personnalisée dépend clairement de notre capacité à créer l'infrastructure et la réceptivité culturelle à ces changements.

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Brief report

Personalized medicine: selected Web resources

Nancy F. Stimson, MLS

Information about personalized medicine abounds, yet it is difficult to comprehensively search for information on this topic due to the broadness of the term "personalized medicine," the variety of terms that are used to describe this concept, the vast amount of pertinent journal articles and Web sites, and the fast pace of developments in this field. A selected list of Web sites is provided as a starting place for information about concepts, terminology, projects, databases, tools, and stakeholders related to personalized medicine.

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Dialogues Clin Neurosci. 2009;11:464-468.

Keywords: *personalized medicine; personalized health care; pharmacogenomics; genomics; Human Genome Project; Web site; internet*

Author affiliations: Biomedical Library, University of California, San Diego, La Jolla, California, USA

Address for correspondence: University of California, San Diego, Biomedical Library, 0699, 9500 Gilman Drive, La Jolla, CA 92093-0699, USA
(e-mail: nstimson@ucsd.edu)

Since the completion of the Human Genome Project in 2003, interest in "personalized medicine" and the quantity of journal literature and Web resources related to this topic has been burgeoning. Former US Department of Health and Human Services (HHS) Secretary, Michael O. Leavitt, made personalized medicine one of his priorities, and the US President, Barack Obama, was the author of the Genomics and Personalized Medicine Acts of 2006 and 2007. The attention and energies of these two high-level officials, as well as many others, have contributed to the continued US support for this research agenda. Kathleen Sebelius succeeded Michael O. Leavitt as HHS Secretary on April 28, 2009. On May 5, 2009, a coalition representing more than a hundred genetic testing laboratories, patient advocates, investors, and health policy researchers sent the Secretary a letter describing their issues and concerns regarding personalized medicine.

As stated on the HHS personalized health care Web site, "Virtually every agency in the US Department of Health and Human Services participates actively in initiatives that are working toward the long-term goals of personalized health care. The integration of these efforts will act as a powerful force to achieve personalized patient care." The HHS issued two reports on US efforts related to personalized medicine. The first report (2007) "included summaries of federal efforts in the areas of expanding the science base for personalized health care; supporting health information technology; regulatory responsibilities; implementing personalized medical products and services in clinical practice; and ethical, legal and social issues." The sec-

ond report (2008) “seeks to bring into focus a sampling of activities that are now underway in different parts of the private and academic health care sectors toward integrating personalized health care into clinical practice.”

- HHS Personalized Health Care Initiative, US Department of Health and Human Services
[<http://www.hhs.gov/myhealthcare/>]
- HHS Secretary's Advisory Committee on Genetics, Health & Society (SACGHS)
[http://oba.od.nih.gov/sacghs/sacghs_home.html]
- "Personalized Health Care: Opportunities, Pathways, Resources," US Department of Health and Human Services, September 2007
[<http://www.hhs.gov/myhealthcare/news/phc-report.pdf>]
- "Personalized Health Care Pioneers, Partnerships, Progress," US Department of Health and Human Services, November 2008
[http://www.hhs.gov/myhealthcare/news/phc_2008_report.pdf]
- Letter to HHS Secretary, Kathleen Sebelius, May 5, 2009
[<http://www.dnapolicy.org/resources/LtrtoSecSebeliusrePersonalizedMedicine.pdf>]

Another important milestone on the road to attaining personalized medicine was the passage of the US Genetic Information Nondiscrimination Act (GINA) which was signed into law in May 2008, and was designed to prohibit the improper use of genetic information in health insurance and employment.

- H.R. 493, Genetic Information Nondiscrimination Act of 2008
[<http://thomas.loc.gov/cgi-bin/bdquery/z?d110:HR00493:@@L&summ2=m&>]

Terminology

How can researchers and clinicians sift through the petabytes of information on the internet to find relevant information about personalized medicine? At the time of writing, a keyword search for “personalized medicine” in PubMed reveals hundreds of articles published in the last year alone, and that reflects just a tiny percentage of the articles on this topic. A Google search for the phrase “personalized medicine” now reveals over 500 000 results

and that, too, is just the tip of the iceberg. Why are these search engines finding such a small percentage of the available information? The concept of personalized medicine is a broad one, and one that can be represented by many different terms and spellings such as personalized medicine, personalised medicine, personalized health care, personalized healthcare, individualized medicine, etc. In addition, there are many narrower topics, or related topics, covered by this umbrella term such as pharmacogenomics, biomarkers, neuromarkers, microarray analysis, single nucleotide polymorphism (SNP) profiling, electronic health records, and many more. The proliferation of “-omics” terms such as genomics, pharmacogenomics, proteomics, epigenomics, nutrigenomics, agrigenomics, metabonomics—even neurogenomics—is one signal of the infiltration of genomics into many different fields.¹ Another indicator is the number of recently published journals specifically dedicated to this topic that were started after 2002 (eg, *Personalized Medicine*, *Current Pharmacogenomics and Personalized Medicine*, *Human Genomics and Proteomics*, *Genome Medicine*, *Genomic Medicine*, *BMC Medical Genomics*, *The Open Genomics Journal*, etc).

When searching PubMed for articles, it is often useful to search using National Library of Medicine Medical Subject Headings (MeSH) which are used to consistently categorize article references, and bring together references on a topic. If there is a good MeSH term (or terms) for a particular topic, researchers do not have to think of every single keyword and synonym that authors might have used to describe that concept. However, there is not a single MeSH term that covers the broad topic of personalized medicine, and existing MeSH terms such as “Pharmacogenetics,” “Patient-Centered Care,” “Genomics,” “Genome, Human,” “Genetics, Medical,” “Proteomics,” “Biomarkers,” and “Medical Records Systems, Computerized” vary in how consistently they are applied.

Definitions of particular terms vary, also. It is hard to find a standard definition of many terms, including “personalized medicine,” and sometimes people confuse one term with another (eg, “pharmacogenetics” vs “pharmacogenomics”).² The issue of terminology concerns everyone: researchers, clinicians, public policy decision makers, bioinformaticists, and laypeople, as well as other stakeholders. The US National Human Genome Research Institute, and US National Cancer Institute have created useful glossaries:

Brief report

- Talking Glossary of Genetic Terms, US National Human Genome Research Institute
[<http://genome.gov/10002096>]
- Dictionary of Cancer Terms, US National Cancer Institute
[<http://www.cancer.gov/dictionary/>]

There is an excellent glossary in the new, comprehensive, two-volume book set, *Genomic and Personalized Medicine*, which was published by Elsevier/Academic Press in 2009.³ This book set, available in print or electronically through ScienceDirect, is an excellent starting place for people who are trying to get an understanding of the many concepts and issues that comprise personalized medicine. The former US HHS Secretary, Michael O. Leavitt, wrote the foreword to this book. Section 12 of this book, titled “Neuropsychiatric Disease Genomic Medicine,” includes eight chapters that discuss dementia, Parkinson’s disease, epilepsy, ophthalmology, neuromuscular disorders, psychiatric disorders, depression, and bipolar disorder.

- *Genomic and Personalized Medicine*
[<http://www.science-direct.com/science/book/9780123694201>]

In short, the terminology that is used in article databases such as PubMed as well as on various Web sites is wide-ranging and makes it difficult to pull all of the relevant information on this topic together.

Additional Web resources

There are thousands of Web sites that pertain to personalized medicine and its subtopics. Any collection, especially one in a “brief report” such as this, is necessarily a “selected” list. The following Web sites are provided as a sample of the range of projects and Web sites that are available:

US National Institutes of Health (NIH)

- National Human Genome Research Institute (NHGRI)
[<http://genome.gov>]
- PhenX Toolkit, NHGRI
[<https://www.phenxtoolkit.org/>]
- ENCODE Project: ENCyclopedia of DNA Elements, NHGRI
[<http://www.genome.gov/ENCODE/>]
- Ethical, Legal, and Social Implications ELSI Research Program, NHGRI
[<http://www.genome.gov/10001618>]
- Human Genome Project, NHGRI
[<http://www.genome.gov/10001772>]
- Pharmacogenetics Research Network, National Institute of General Medical Sciences (NIGMS)
[<http://www.nigms.nih.gov/pharmacogenetics>]
- Environmental Genome Project, National Institute of Environmental Health Sciences (NIEHS)
[<http://www.niehs.nih.gov/research/supported/programs/egp/>]
- NIH Chemical Genomics Center
[<http://www.ncgc.nih.gov/>]
- NIH Data Sharing Policy for Genome Wide Association Studies (GWAS)
[<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html>]
- NIH Roadmap for Medical Research
[<http://nihroadmap.nih.gov>]

NIH neurosciences-related resources

- NIH Blueprint for Neuroscience Research
[<http://neuroscienceblueprint.nih.gov/>]
- National Institute of Neurological Disorders and Stroke (NINDS): Clinical and Translational Resources
[http://www.ninds.nih.gov/research/scientific_resources/clinical/]
- Neuroscience Information Framework (NIF)
[<http://www.neuinfo.org/>]

National Center for Biotechnology Information (NCBI) databases

- Entrez - All Databases
[<http://www.ncbi.nlm.nih.gov/sites/gquery>]
- Human Genome Resources
[<http://www.ncbi.nlm.nih.gov/projects/genome/guide/human/>]
- Online Mendelian Inheritance in Man (OMIM)
[<http://www.ncbi.nlm.nih.gov/omim/>]
- Entrez Gene
[<http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene>]
- Database of Genotypes and Phenotypes (dbGaP)
[<http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap>]

- Gene Expression Omnibus
[<http://www.ncbi.nlm.nih.gov/geo/>]
- PubChem
[<http://pubchem.ncbi.nlm.nih.gov/>]
- NCBI BioSystems
[<http://www.ncbi.nlm.nih.gov/biosystems/>]

Other US federal government agency resources

- HHS Personalized Health Care: Federal Activities
[<http://www.hhs.gov/myhealthcare/activities/>]
- HHS CDS Collaboratory
[http://healthit.hhs.gov/portal/server.pt?open=512&objID=1230&parentname=CommunityPage&parentid=1&mode=2&in_hi_userid=10741&cached=true]
- CDC Public Health Genomics
[<http://www.cdc.gov/genomics/>]
- CDC Evaluation of Genomic Applications in Practice and Prevention Initiative
[<http://www.cdc.gov/genomics/gtesting/EGAPP/about.htm>]
- CDC Human Genome Epidemiology Network (HuGENet)
[<http://www.cdc.gov/genomics/hugenet/default.htm>]
- CDC HuGE Navigator
[<http://www.hugenavigator.net/>]
- CDC Genomics Workforce Competencies
[<http://www.cdc.gov/genomics/training/competencies/>]

Nonprofit organizations

- Personalized Medicine Coalition
[<http://www.personalizedmedicinecoalition.org/>]
- Genetic Alliance
[<http://www.geneticalliance.org/>]
- Coalition for 21st Century Medicine
[<http://www.twentyfirstcenturymedicine.org/index.shtml>]

Resources for the general public

- Genetics Home Reference
[<http://ghr.nlm.nih.gov/>]
- "From Genes to Personalized Medicines," National Institutes of Health
[http://www.nih.gov/about/researchresultsforthe public/Genes_PersonalizedMed.pdf]

- "Genetics, Disease Prevention and Treatment," National Human Genome Research Institute (NHGRI)
[<http://www.genome.gov/19016938>]
- MedlinePlus: Genes and Gene Therapy
[<http://www.nlm.nih.gov/medlineplus/genesandgenetherapy.html>]

Commercial companies targeting the general public

- deCODEme
[<http://www.decodeme.com/>]
- 23andMe
[<https://www.23andme.com/>]
- Navigenics
[<http://www.navigenics.com/>]

Miscellaneous resources

- Morningside Initiative, American Medical Informatics Association (AMIA)
[<http://www.amia.org/inside/initiatives/cds>]
- "The Roadmap for National Action on Clinical Decision Support," AMIA
[<http://www.amia.org/files/cdsroadmap.pdf>]
- National Coalition for Health Professional Education in Genetics (NCHPEG)
[<http://www.nchpeg.org>]
- BIG Health Consortium
[<http://bighealthconsortium.org/>]
- J. Craig Venter Institute
[<http://www.jcvi.org/>]
- UCSC Genome Bioinformatics
[<http://genome.ucsc.edu/>]
- GenMAPP: Gene Map Annotator and Pathway Profiler
[<http://www.genmapp.org/>]
- Bioconductor: Open Source Software for Bioinformatics
[<http://www.bioconductor.org/>]
- Brain Research and Integrative Neuroscience Network (BRAINet)
[<http://brainnet.net/>]
- Allen Brain Atlas, Allen Institute for Brain Science
[<http://www.brain-map.org/>]

Although this article focuses primarily on US projects and Web sites, progress towards making personalized

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medicine a reality is an international effort, as is reflected by this sample of project and tool Web sites:

International and non-US resources

- 1000 Genomes Project
[<http://www.1000genomes.org/page.php>]
- Human Variome Project
[<http://www.humanvariomeproject.org/>]
- International HapMap Project
[<http://www.hapmap.org/index.html.en>]
- Structural Genomics Consortium
[<http://www.thesgconline.org/>]
- GeneCards
[<http://www.genecards.org/>]
- Ensembl Human Genome Browser
[http://www.ensembl.org/Homo_sapiens/Info/]
- ArrayExpress Database
[<http://www.ebi.ac.uk/microarray-as/ae/>]
- International Sequencing Consortium
[<http://www.intlgenome.org/>]
- European Bioinformatics Institute
[<http://www.ebi.ac.uk/>]
- Swiss Institute of Bioinformatics
[<http://www.isb-sib.ch/>]
- Max Planck Institute for Molecular Genetics
[<http://www.molgen.mpg.de/>]
- Nationales Genomforschungsnetz (NGFN)
[<http://www.ngfn.de/>]
- Riken Genomic Sciences Research Complex (GSC)
[<http://www.gsc.riken.go.jp/>]
- Kyoto Encyclopedia of Genes and Genomes
[<http://www.genome.jp/kegg/>]

- ExPASy Proteomics Server
[<http://expasy.org/>]
- European Proteomics Association (EuPA)
[<http://www.eupa.org/>]
- HUPO: Human Proteome Organisation
[<http://www.hupo.org/>]
- HUPO Brain Proteome Project
[<http://www.hbpp.org/5602.html>]

Conclusion

Learning about the plethora of concepts, terminology, projects, databases, tools, and stakeholders involved in personalized medicine is a difficult task. For an overview with both breadth and depth, consulting the book by Willard and Ginsburg (mentioned above)³ is highly recommended. Keeping up with new literature and other developments in specific areas of personalized medicine is also challenging. It is possible to follow new journal literature, in PubMed for example, by setting up search alerts for topics of interest, or alerts for tables of contents from particular journals. Another strategy is to create Google alerts, or to arrange with government agencies or other organizations to receive their news alerts. While e-mail alerts are one way to receive this information, an RSS (Really Simple Syndication) reader such as Google Reader (<http://reader.google.com>) is another way to easily and efficiently read and manage alerts. Researchers at institutions that are fortunate enough to have a librarian or other information professional should consult them for advice on searching for information, managing what they find, and keeping informed about new developments, especially in fast-paced fields such as personalized medicine. □

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2. de Leon J. The future (or lack of future) of personalized prescription in psychiatry. *Pharmacol Res*. 2009;59:81-89.
3. Willard HF, Ginsburg GS, eds. *Genomic and Personalized Medicine*. 1st ed. Amsterdam, the Netherlands; Boston, MA: Elsevier/Academic Press; 2009.

Medicina personalizada: recursos seleccionados de la web

Aunque existe bastante información acerca de la medicina personalizada, todavía es difícil buscar de manera comprensible información sobre este tema debido a la amplitud del término "medicina personalizada", la variedad de términos que se utilizan para describir este concepto, la gran cantidad de artículos de revistas y sitios web, y el rápido avance del progreso en este campo. Se provee una lista seleccionada de sitios web como punto de partida para obtener información acerca de conceptos, terminología, proyectos, bases de datos, herramientas y usuarios relacionados con la medicina personalizada.

Médecine personnalisée : sélection de sources internet

Le terme de « médecine personnalisée » est si large qu'il est difficile d'effectuer une recherche complète sur ce sujet qui regorge d'informations, qui est décrit par une multitude de mots dans une grande quantité d'articles de journaux et de sites internet appropriés et dont le développement est rapide. Nous avons sélectionné une liste de sites internet qui permettent de débiter une recherche sur les concepts, la terminologie, les projets, les données, les outils et les partenaires de la médecine personnalisée.

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- Epilepsy and Psychiatry
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